UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Chemical Safety and Pollution Prevention

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: December 15, 2011.

SUBJECT: Pyroxasulfone. Application for Section 3 Registration for Use on Corn, Soybean, and Wheat. Summary of Analytical Chemistry and Residue Data.

PC Code: 090099
Decision No.: 409018
Petition No.: 9F7560
Risk Assessment Type: NA
TXR No.: NA
MRID No.: See MRID Summary Table

DP Barcode: D365229, D371257
Registration No.: 63588-OE, 63588-OG and 63588-OR
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 447399-55-5
40 CFR: 180.[redacted]

Ver.Apr.08

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DEC 19 RECD, 2011

MRID Summary Table		
MRID No.	**Study Type**	**Monograph Section(s); Comments**
47701649 48430006	860.1300 Corn	B.7.1.1
47701650	860.1300 Soybean	B.7.1.2
47701651	860.1300 Hen	B.7.2.1
47701652	860.1300 Hen	B.7.2.1
47701653	860.1300 Goat	B.7.2.2
47701654	860.1300 Goat	B.7.2.2
47701655	860.1300 Goat	B.7.2.2
47701656 48430001 48430011	860.1340 Corn commodities 860.1380 Corn commodities 860.1500 Field and sweet corn 860.1520 Field corn	B.5.2.1 B.7.6.2 B.7.6.1.1 B.7.6.1.1, B.7.7.2
47701657	860.1340 Soybean commodities 860.1380 Soybean commodities 860.1500 Soybean 860.1520 Soybean	B.5.2.1 B.7.6.2 B.7.6.1.2 B.7.6.1.2, B.7.7.2
47701658	860.1340 Wheat commodities	B.5.2.1
47701659	860.1340 Cattle commodities 860.1380 Cattle commodities 860.1480 Cattle	B.5.2.2 B.7.8.3 B.7.8.2
47701660	860.1340 Poultry egg	B.5.2.2
47701661	860.1340 Independent laboratory validation; corn commodities	B.5.2.1
47701662	860.1340 Independent laboratory validation; soybean commodities	B.5.2.1
47701663	860.1340 Independent laboratory validation; cattle commodities	B.5.2.2
47701664	860.1340 Independent laboratory validation; poultry egg	B.5.2.2
47701665	860.1340 Radiovalidation	B.5.2.3
47701669	860.1500 Wheat	B.7.6.1.3
47701670	860.1500 Wheat	B.7.6.1.3
47701673	860.1360 Multiresidue methods	B.5.2.4
47701674	860.1850 Confined rotational crops	B.7.9.1
47701675	860.1900 Field pea	B.7.9.2
47701676	860.1900 Field pea	B.7.9.2

This document was originally prepared under contract by Dynamac Corporation (1901 Research Boulevard, Suite 220; Rockville, MD 20850.

The document has been reviewed by the HED and revised to reflect current Office of Chemical Safety and Pollution Prevention (OCSPP) policies.

Executive Summary

Pyroxasulfone is a new herbicide belonging to the pyrazole class of selective herbicides. It provides contact and residual control of a broad spectrum of broadleaf weeds and grasses, including glyphosate-resistant varieties. Pyroxasulfone acts as a potential inhibitor of very-long-chain fatty acid (VLCFA) biosynthesis, similar in mode to the K3 group of herbicides (Group 15).

Under PP#9F7560, K-I Chemical, U.S.A. Inc. is proposing tolerances for combined residues of the herbicide, pyroxasulfone [3-[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)pyrazol-4-yl methylsulfonyl]-4,5-dihydro-5,5-dimethyl-1,2-oxazole], and its major metabolites, M-1, M-3, and M-25 calculated as pyroxasulfone equivalents in/on the following commodities:

Field Corn Kernel	0.01 ppm
Field Corn Forage	0.15 ppm
Field Corn Stover	0.15 ppm
Sweet Corn Ears	0.02 ppm
Sweet Corn Forage	0.15 ppm
Sweet Corn Stover	0.15 ppm
Field Corn Grits	0.01 ppm
Field Corn Meal	0.01 ppm
Field Corn Flour	0.01 ppm
Field Corn Starch	0.01 ppm
Field Corn Oil (wet and dry milled)	0.01 ppm
Wheat Grain	0.02 ppm
Wheat Forage	0.20 ppm
Wheat Straw	0.20 ppm
Soybean Seed	0.05 ppm
Soybean Forage	1.0 ppm
Soybean Hay	2.0 ppm
Soybean Meal	0.05 ppm
Soybean Hulls	0.02 ppm
Soybean Refined oil	0.01 ppm

Review of the submitted petition is being conducted as a tri-lateral review work-share effort which will be carried out in part with Canada (PMRA) and Australia (APVMA).

In conjunction with this petition, K-I Chemical is requesting registration of two new products containing pyroxasulfone, Pyroxasulfone 85 WG Herbicide, an 85% water-dispersible granule (WG) formulation (EPA File Symbol 63588-OE), and V-10233 Herbicide, a 42.5% WG formulation (EPA File Symbol 63588-OG). The products are proposed for use on field corn, sweet corn, pop corn, soybean, and wheat. Applications to field corn, sweet corn, pop corn, and soybean are to be made preplant, preemergence, or early postemergence at 0.08-0.21 lb ai/A (depending on soil texture) with a maximum seasonal rate of 0.267 lb ai/A; pre-harvest intervals (PHIs) and/or pre-grazing intervals (PGIs) of 7-37 days have been proposed. Application to wheat is to be made as a single preplant or preemergence application at 0.05-0.11 lb ai/A (depending on soil texture) with a 42-day PGI.

The nature of the residue in plants is tentatively adequately understood based on metabolism studies with field corn and soybeans; additional data pertaining to immature soybean crop commodities along with additional storage stability related data are needed. The nature of the

residue in rotational crops is adequately understood based on confined rotational crop studies with rotated soybean, radish, and wheat. The metabolic pathway of pyroxasulfone is similar in primary and rotational crops, and mainly involves cleavage of the methyl sulfone bridge of the parent compound, oxidation and/or demethylation of the pyrazole cleavage product to yield metabolites M-1 and M-25, and reaction of the isoxazoline cleavage product with cysteine and/or glutathione; further demethylation, deamination, and/or conjugation of these metabolites occurs, yield additional metabolites including M-3. HED Residues of Concern Knowledge-Base Subcommittee (ROCKS) has determined that the residues of concern in crop commodities for risk assessment and tolerance enforcement in the U.S. are pyroxasulfone and its metabolites M-1, M-3, and M-25 in corn and wheat. RABIV has concluded the residues of concern for corn grain are parent and M-3. Thus, the residue definition for corn grain will be harmonized with Canada as well as the tolerance value. The residues of concern in soybean for risk assessment in the U.S. are pyroxasulfone and its metabolites M-1, M-3, M-25, and M-28. The residues of concern in soybean for tolerance enforcement in the U.S. are pyroxasulfone and its metabolites M-1, M-3, M-25. M-28 may need to be included pending reanalysis of the soybean seed samples for M-28.

The nature of the residue in livestock is adequately understood based on metabolism studies with goats and hens. Metabolism of pyroxasulfone in livestock occurs primarily via cleavage between the rings, to form metabolites M-1, M-8, M-10, and/or M-15, followed by oxidation, to yield metabolite M-3, and/or demethylation, to yield metabolites M-12 and M-9. The parent compound may also undergo demethylation, hydroxylation followed by oxidation, or oxidation followed by ring cleavage. HED has determined that the residues of concern in livestock commodities for tolerance enforcement in the U.S. are pyroxasulfone and its metabolites M-1, and M-3. Residues of concern in livestock commodities for risk assessment in the U.S. are pyroxasulfone and its metabolites M-1, M-3, M-25, and M-28.

The petitioner has proposed high performance liquid chromatography/triple quadrupole mass spectrometry (LC/MS/MS) methods for the enforcement of tolerances for pyroxasulfone residues in/on crop commodities. The methods are adequate to determine residues of pyroxasulfone and metabolites M-1, M-3, and M-25 in corn, soybean, and wheat commodities. The methods have been modified to include the recommendations of the independent laboratory which were 1) include instructions for reporting metabolite residues in parent equivalents, 2) include a warning that emulsions may form, and 3) include the procedures for analysis of wheat commodities. The validated limit of quantitation (LOQ) is 0.005 ppm for each analyte in corn and soybean commodities, with the exception of M-3 in corn meal and M-1 in corn oil, soybean seed, and soybean meal, for which the LOQ is 0.01 ppm. The proposed enforcement methods for crop commodities have been deemed acceptable by the Analytical Chemistry Branch of the Biological and Economic Analysis Division (ACB) by HED using ACB SOP 19. Since no tolerances are needed for meat, milk, poultry and eggs due to the corn use, no enforcement method for livestock commodities is needed. However, in the future a livestock enforcement method may be required. Adequate LC/MS/MS methods were used for data collection for crop and livestock commodities. The data indicate that the PAM Vol. I multiresidue methods, including Protocol D (report IIA 4.3/14) and Protocols E and F (report IIA 4.3/11) may be applicable for determination of pyroxasulfone *per se*; however, the FDA multiresidue methods are not suitable for determination of the metabolites M-1, M-3, and M-25.
Pyroxasulfone (KIH-485) and metabolites M-1 and M-3 were found to be stable in corn stover through 12 months of frozen storage and in corn grain and forage through 13 months of frozen

storage. Pyroxasulfone, M-1, and M-3 were found to be stable in corn processed commodities during 6 months (oil) or 7 months (starch, flour, and meal) of frozen storage. M-25 residues were stable in forage for 24 months, grain for 26 months, stover for 25 months, starch for 16 months, flour for 23 months, and meal for 18 months. M-25 residues in com oil were moderately stabile at 67% remaining after 17 months of frozen storage.

Pyroxasulfone was found to be stable in soybean forage and hay through as much as 17 months of storage, where no significant degradation of the residue was observed. Pyroxasulfone was found to be stable for up to 19 months frozen storage in seed, up to 7 months in refined oil, and up to 10 months storage in meal and hulls. M-1 was found to be stable in forage and hay for up to 17 months, up to 6 months in seed, up to 7 months in oil, and up to 10 months in meal and hulls. M-1 declined by approximately 40% in soybean seed at 19 months of frozen storage. M-3 was found to be stable in forage and hay up to a 17-month period of storage up to a 19-month storage interval in seed, and up to 10 months in oil, meal, and hulls. Some decline in M-1 and M-3 was detected within 7 months and 10 of frozen storage, respectively, in refined oil, while both analytes were found to be stable in meal and hulls for up to 10 months of frozen storage. M-25 was found to be stable in forage hay, and seed after 12 months of frozen storage, in oil after 13 months of frozen storage, and in hulls and meal after 14 months of frozen storage.

For M-25, the longest storage interval samples of soybean processed commodities (24-26 months) remained to be analyzed at the time this report was finalized. The petitioner stated that this will be reported in a future report amendment.

An adequate cattle feeding study has been submitted. The data indicate that tolerances for livestock commodities are not needed to support the proposed pyroxasulfone uses. A poultry feeding study is not needed at this time.

Pending amendment of the proposed labels, adequate field trial data have been submitted for field corn and sweet corn. Soybean seed samples are required to be reanalyzed for M-28. The submitted field trial data for wheat reflect studies conducted in Australia and do not include residue data for wheat hay. HED has concluded that the Australian wheat data may be used to partially fulfill field trial data requirements for wheat; additional data from field trials conducted in the U.S., which include data for wheat hay, must be submitted. Adequate field trial data are available to support the proposed tolerances for: corn, field, grain; corn, field, forage; corn, field, stover; corn, sweet, kernel plus cob with husks removed (K+CWHR); corn, sweet forage; corn, sweet, stover. The data indicate that the proposed tolerance for field corn grain is too low; tolerance of 0.015 ppm would be appropriate. The data indicate that the proposed tolerances for field corn forage and sweet corn forage are too high; tolerances of 0.06 ppm and 0.10 ppm, respectively, would be appropriate. The available processing data indicate that no tolerances are needed for pyroxasulfone residues in field corn processed commodities.

No residue data were submitted to support the proposed uses on popcorn. The submitted data for field corn may be translated to popcorn because the proposed uses on all types of corn (field, pop, and sweet) are identical. Tolerances are needed for popcorn commodities, at 0.015 ppm for popcorn grain and 0.15 ppm for popcorn stover.

Pending submission of additional storage stability data for processed commodities of soybean, adequate processing studies have been submitted for field corn and soybean. No processing

study was submitted for wheat; a processing study is required. The adequacy of proposed tolerances for soybean raw agricultural commodities (RACs) and soybean processed commodities will be evaluated pending submission of the final reports of the storage stability studies and additional residue data. In addition, soybean processing data on the metabolite M-28 may be needed if it is determined to be a residue of concern.

The petitioner has proposed an 18-month plantback interval (PBI) for all crops not on the label, based on the results of the confined rotational crop study, which indicated the potential for quantifiable residues of concern in/on rotated radish, soybean, and wheat commodities from 30- and 120-day PBIs; and in rotated soybean and wheat commodities from a 365-day PBI. The results of the confined rotational crop study indicate that no quantifiable pyroxasulfone residues of concern would be expected in root crops planted 12 months following treatment at 1x; however, no data are available demonstrating that residues of concern will be below the LOQ in/on other rotated crop commodities at a PBI of 18 months. A limited field rotational crop study must be submitted. The study must be conducted in the U.S. and should reflect application at the maximum proposed seasonal rate (0.267 lb ai/A) and planting of rotated crops at plantback intervals of 1, 6, and 12 months. If quantifiable residues are found at the 12-month, then, extensive field trials will be required to set rotational crop tolerances. Until the required rotational crop data have been submitted, the petitioner must modify the labels for both products to specify that only root crops and crops on the label may be planted after pyroxasulfone application; crops on the label may be planted any time after application, and root crops may be planted 12 months after application.

One of the two products associated with this petition is a multiple active ingredient (MAI) product; the 42.5% WG formulation contains flumioxazin in addition to pyroxasulfone. The subject review only addresses the adequacy of the available data to support the proposed uses of pyroxasulfone. The adequacy of available or concurrently submitted data to support the proposed uses of flumioxazin is not addressed herein.

Regulatory Recommendations and Residue Chemistry Deficiencies

HED has examined the residue chemistry database for pyroxasulfone. Pending submission of a revised Section B (see requirements under Directions for Use), a revised Section F (see requirements under Proposed Tolerances), and analytical reference standards (see requirements under Submittal of Analytical Reference Standards), there are no residue chemistry issues that would preclude granting conditional Section 3 registration for the requested uses of pyroxasulfone, or establishment of tolerances for residues of pyroxasulfone as follow:

> Tolerances are established for residues of the herbicide pyroxasulfone, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of pyroxasulfone [3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole] and its metabolite, 5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-carboxylic acid (M-3) calculated as the stoichiometric equivalent of pyroxasulfone, in or on the commodity.
>
> Corn, field, grain.....0.015 ppm
> Corn, sweet, kernel plus cob with husks removed.....0.015 ppm

Corn, pop, grain .....0.015 ppm

Tolerances are established for residues of the herbicide pyroxasulfone, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of pyroxasulfone [3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole] and its metabolites [5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid (M-1), 5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-carboxylic acid (M-3), and [5-(difluoromethoxy)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid (M-25), calculated as the stoichiometric equivalent of pyroxasulfone, in or on the commodity.

Corn, field, forage .....0.06 ppm
Corn, field, stover .....0.15 ppm
Corn, sweet, forage .....0.10 ppm
Corn, sweet, stover .....0.15 ppm
Corn, pop, stover .....0.15 ppm

A human health risk assessment is forthcoming.

860.1200 Directions for Use

- The product labels for the 85% WG and 42.5% WG formulations should be amended to remove any mention of soybean and wheat, since these uses are not being recommended for registration.

- The petitioner must amend the product label for the 85% WG formulation to specify the following maximum seasonal application rates: (1) 0.268 lb ai/A for field and sweet corn grown in fine-, medium-fine-, and medium-textured soils; (2) 0.148 lb ai/A for field and sweet corn grown in coarse-textured soils.

- The product label for the 42.5% WG formulation must be amended to specify a maximum seasonal rate for field corn. Because application rates on this product are not dependent on soil type, the proposed maximum seasonal must be $\leq$0.148 lb ai/A.

- The petitioner must amend the product label for the 85% WG formulation to specify that no more than one application may be made in the spring to corn.

- A label statement prohibiting the use of an adjuvant for post-emergent application to corn must be added to the label for the 42.5% WG formulation, since no residue data was submitted to support the use of an adjuvant.

- The 42.5% WG formulation, which is only proposed for application to field corn, includes a restriction against the grazing of treated fields or feeding of treated forage or hay to livestock. HED does not believe that a restriction against the grazing or feeding of treated field corn forage or stover is practical; therefore, the restriction must be removed.

- The proposed rotational crop restrictions for the 85% WG and 42.5% WG formulations are not supported by the available rotational crop data. Until the required rotational crop data have been submitted, the petitioner must modify the labels for both products to specify that only crops on the label may be planted after pyroxasulfone application; crops on the label may be planted any time after application and root crops after 12 months.

860.1550 Proposed Tolerances

- Proposed tolerances for the following commodities are too low; increased tolerances must be proposed:
  - field corn grain (0.015 ppm)

- Proposed tolerances for the following commodities are too high; reduced tolerances must be proposed:
  - field corn forage (0.06 ppm)
  - sweet corn forage (0.10 ppm)

- Proposed tolerances for field corn processed commodities (grits, meal, flour, starch, dry milled oil, and wet milled oil) are not needed and should be removed from the list of proposed tolerances.

- The following tolerances must be proposed to support the requested uses on popcorn:
  - popcorn grain (0.015 ppm)
  - popcorn stover (0.15 ppm)

- Proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 10.

860.1650 Submittal of Analytical Reference Standards

- Analytical standards for pyroxasulfone and its metabolites M-1, M-3, and M-25 are not currently available in the EPA National Pesticide Standards Repository. Analytical reference standards of pyroxasulfone and metabolites M-1, M-3, and M-25 must be supplied and supplies replenished as requested by the Repository.

Once revised Sections B and F are submitted and analytical standards for residues contained in the tolerance expression, HED can recommend for an unconditional registration for the requested use on corn. HED cannot at this time recommend for registration for the requested uses on soybean and wheat due to outstanding residue chemistry data.

860.1300 Nature of the Residue - Plants

- For the soybean study, residues in the immature commodities soybean forage (foliage collected at first flower) and hay (foliage collected at mid-fruit) were not sufficiently

characterized/identified. Nonextractable residues in these commodities were 13-26% TRR (0.092-0.811 ppm). Additional attempts should be made to release radioactivity, such that nonextractable residues are <10% TRR or <0.05 ppm.

- The petitioner must provide additional information pertaining to storage stability for the soybean metabolism study. The dates of sample extraction and analysis should be provided for all samples, including the samples that were re-extracted for storage stability confirmation. These data will allow HED to determine whether the data are sufficient to determine that the identity of residues did not change during the period between collection and final analysis. In addition, supporting storage stability data will be needed for the required additional analyses for immature foliage matrices.

860.1340 Residue Analytical Methods

Livestock commodities

- Radiovalidation data must be submitted for the method for livestock.

860.1380 Storage Stability

Crop commodities

- Final reports of the ongoing storage stability studies must be submitted. The final reports should include data for M-25 in soybean processed commodities reflecting intervals of up to 16 months for oil, 17 months for hulls, and 19 months for meal.

- With submission of the final reports, the petitioner should include additional information/data pertaining to the procedures used for the storage stability studies, including identification of the fortification levels for each analyte in each matrix, a correct listing of the fortification dates (and storage intervals) for each of the spiked samples, and a discussion of any problems encountered during completion of the studies. An explanation should be provided for not using the data from the 3-month storage interval for M-1 in soybean forage. All residue data spreadsheets for storage stability analyses should be provided.

860.1500 Crop Field Trials

Soybean

- Soybean seed samples need to be reanalyzed for metabolite M-28.

Wheat

- The petitioner must submit 16 additional field trials on wheat, conducted in Zones 2 (1 trial), 5 (5 trials), 7 (5 trials), 8 (4 trials), and 11 (1 trial). In these trials, the petitioner should collect and analyze samples of wheat forage, hay, grain, and straw; samples should be collected at normal harvest times, and the crop growth stage at harvest should be

reported for each sample. The texture of the soil should be reported for each of the field trial sites. If these residue data show that residue levels in forage, grain, and straw are similar to those found in the Australian field trials, HED will not require additional field trial data for wheat hay (i.e., the 16 field trials conducted in the U.S. for wheat hay will be considered sufficient to support a tolerance).

- The study submissions for wheat included no raw data for the analytical portion of the study. Raw data from the sample analyses must be submitted; these data should include sample extraction and analysis dates to allow HED to verify sample storage intervals.

860.1520 Processed Food and Feed

- A processing study must be submitted for wheat.

860.1900 Field Accumulation in Rotational Crops

- The petitioner must submit a limited field rotational crop study with pyroxasulfone. The study must be conducted in the U.S. and should reflect application at the maximum proposed seasonal rate (0.267 lb ai/A) and planting of rotated crops at plantback intervals of 1, 6, and 12 months. If quantifiable residues are found at the 12-month, then, extensive field trials will be required to set rotational crop tolerances. Pyroxasulfone, M-1, M-3, M-25, M-28, and Metabolite C must be determined in these studies. Based on the results of the confined rotational crop study, the limited field rotational crop study does not need to include a root crop.

Background

Pyroxasulfone is a new herbicide in the pyrazole class of selective herbicides. It provides contact and residual control of a broad spectrum of broadleaf weeds and grasses, including glyphosate-resistant varieties. Pyroxasulfone acts as a potential inhibitor of VLCFA biosynthesis similar in mode to the K3 group of herbicides (Group 15). Pyroxasulfone has little effect on germination, yet potentially inhibits shoot elongation of the germinating seed. Pyroxasulfone is translocated in plants through xylem and is apoplastic. K-I Chemical is proposing pyroxasulfone for use on field corn, sweet corn, pop corn, soybean, and wheat in the U.S. The chemical structure and nomenclature of pyroxasulfone and its metabolites proposed for regulation are presented in Table 1, and the physicochemical properties of the technical grade of pyroxasulfone are presented in Table 2. This petition represents the first food/feed uses of pyroxasulfone proposed in the U.S.

The chemical names and structures of pyroxasulfone metabolites are presented in Appendix 1.

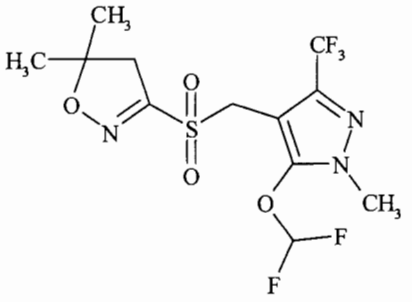
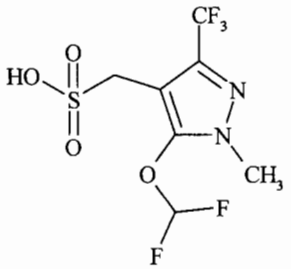
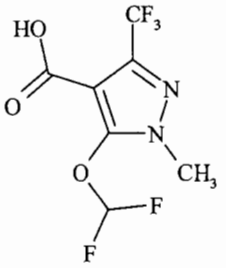
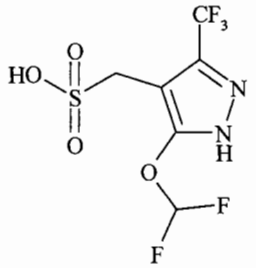
Table 1. Pyroxasulfone Nomenclature.	
Chemical structure of Pyroxasulfone	
Common name	Pyroxasulfone
Company experimental name	KIH-485; AE 2196191
IUPAC name	3-[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)pyrazol-4-ylmethylsulfonyl]-4,5-dihydro-5,5-dimethyl-1,2-oxazole
CAS name	3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole
CAS registry number	447399-55-5
End-use product (EP)	Pyroxasulfone 85 WG Herbicide (85% WG; EPA File Symbol 63588-OE) V-10233 Herbicide (42.5% WG; EPA File Symbol 63588-OG)
Chemical structure of M-1 metabolite	 [5-(difluoromethoxy)-l-methyl-3-(trifluoromethyl)-l*H*-pyrazol-4-yl)]methanesulfonic acid
Chemical structure of M-3 metabolite	 5-(difluoromethoxy)-l-methyl-3-(trifluoromethyl)-l*H*-pyrazole-4-carboxylic acid
Chemical structure of M-25 metabolite	 [5-(difluoromethoxy)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)]methanesulfonic acid

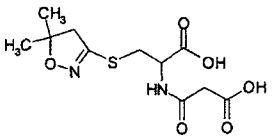
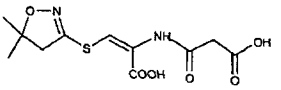
Table 1. Pyroxasulfone Nomenclature.	
Chemical structure of M-28 metabolite	 3-[1-Carboxy-2-(5,5-dimethyl-4,5-dihydroisoxazol-3-ylthio)ethylamino]-3-oxopropanoic acid
Chemical structure of Metabolite C	 None provided (malonyl dehydrogenated cysteine derivative of isoxazoline group)

Table 2. Physicochemical Properties of Pyroxasulfone.		
Parameter	Value	Reference[1]
Melting point	130.7 °C	MRID 47701615
pH	5.03 at 22 °C	MRID 47701613
Density	1.60 g/cM-3	MRID 47701616
Water solubility	3.49×10^{-3} g/L at 20.0 ± 0.5 °C	MRID 47701619
Solvent solubility	g/L at 20 °C Methanol: 11.4 Acetone: > 250 Ethyl acetate: 97.0 n-Hexane: 0.0721 Toluene: 11.3 Dichloromethane: 151	MRID 47701620
Vapor pressure	2.4×10^{-6} Pa at 25 °C	MRID 47701621
Dissociation constant, pK_a	Not applicable (pyroxasulfone N-containing rings are not expected to be protonated in a practical pH range)	MRID 47701617
Octanol/water partition coefficient, $Log(P_{OW})$	log P_{OW} = 2.39 at 25 °C, pH 8.7	MRID 47701618
UV/visible absorption spectrum	at pH 1.13: λ_{max} = 225.5 nm; ε = 7291 $Lmol^{-1}cm^{-1}$ at pH 7.23: λ_{max} = 225.0 nm; ε = 7340 $Lmol^{-1}cm^{-1}$ at pH 10.91: λ_{max} = 225.5 nm; ε = 7334 $Lmol^{-1}cm^{-1}$	MRID 47701614

[1] As reported in "Pyroxasulfone Annex IIA, Section 1, Points 1, 2, 3 and 9" (Tier II - Document M-II).

860.1200 Directions for Use

The petitioner has submitted undated draft specimen labels for the 85% WG (Pyroxasulfone 85 WG Herbicide; EPA File Symbol 63588-OE) and 42.5% WG (V-10233 Herbicide; EPA File Symbol 63588-OG) formulations of pyroxasulfone. The 42.5% WG formulation is an MAI product that also contains flumioxazin at 33.5%.

A summary of the proposed use patterns on corn, soybean, and wheat are presented in Table 3.

Table 3. Summary of Directions for Use of Pyroxasulfone.[1]

Applic. Timing, Type, and Equip.	Formulation [EPA File Symbol]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Corn (Field, Pop, Sweet, and Seed)						
Fall application Broadcast Ground	85% WG [63588-OE]	C: NA M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS	0.267	37 (sweet corn ears)	Application may be made in the fall to minimum or no tillage fields to be planted to corn the following spring.
Preplant Broadcast surface or incorporated Ground	85% WG [63588-OE]	C: 0.08-0.11 M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS			Surface application may be made up to 45 days prior to planting, and soil incorporated application may be made up to 14 days prior to planting.
Preemergence Broadcast Ground	85% WG [63588-OE]	C: 0.08-0.11 M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS			
Early postemergence Broadcast Ground	85% WG [63588-OE]	C: 0.08-0.11 M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS			Application may be made up to V4 stage (visible 4th leaf collar). A 7-day pregrazing interval (PGI) is proposed for corn or corn forage.
Corn (Field)						
Fall application Broadcast Ground or aerial	42.5% WG [63588-OG]	0.08-0.12	NS	NS	NS	Application may be made in the fall to minimum or no tillage fields to be planted to corn the following spring.
Preplant Broadcast Ground or aerial	42.5% WG [63588-OG]	0.08-0.12	NS			Corn must be planted within 7-30 days after application.

Table 3. Summary of Directions for Use of Pyroxasulfone.[1]

Applic. Timing, Type, and Equip.	Formulation [EPA File Symbol]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Soybeans						
Fall application Broadcast Ground	85% WG [63588-OE]	C: NA M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS	0.267	15 (seed)	Application may be made in the fall to minimum or no tillage fields to be planted to soybean the following spring.
Preplant Broadcast surface or incorporated Ground	85% WG [63588-OE]	C: 0.08-0.11 M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS			Surface application may be made up to 45 days prior to planting, and soil incorporated application may be made up to 14 days prior to planting.
Preemergence Broadcast Ground	85% WG [63588-OE]	C: 0.08-0.11 M: 0.11-0.15 MF: 0.15-0.19 F: 0.19-0.21	NS			
Early postemergence Broadcast Ground	85% WG [63588-OE]	C: 0.08 M: 0.08-0.11 MF: 0.11-0.15 F: 0.15-0.19	NS			Application may be made from the first- to third-trifoliate leaf stage. A 7-day PGI is proposed for soybean or soybean forage, hay, or straw.
Fall application Broadcast Ground or aerial	42.5% WG [63588-OG]	0.08-0.12	NS	0.12	NS	Application may be made in the fall to fields to be planted to soybean the following spring.
Preplant or preemergence Broadcast or banded Ground or aerial	42.5% WG [63588-OG]	0.08-0.12	NS			Preemergence application is to be made within 3 days of planting. May be applied to soils containing up to 5% organic matter.
Wheat (fall or winter-seeded wheat)						
Preplant or preemergence Broadcast Ground	85% WG [63588-OE]	C, M: 0.05-0.08 MF, F: 0.08-0.11	1	0.267	NS	Preplant application may not be made more than 14 days prior to planting. Application to durum wheat is prohibited. A 42-day PGI is proposed for wheat or wheat forage, hay, or straw.

[1] C = Coarse soil texture; M = Medium soil texture; MF = Medium-fine soil texture; F = Fine soil texture. NA = Not applicable. NS = Not specified.

For the 85% WG formulation, the proposed label specifies that the product may only be applied using ground equipment. Application through any type of irrigation system is prohibited. Applications are to be made in a minimum of 10 gal/A. Application of the 85% WG formulation to peat or muck soils or soils with ≥10% organic matter is prohibited. The 85% WG formulation may be impregnated or coated onto dry bulk granular fertilizer for fall and preplant surface and preplant incorporated applications.

The label for the 42.5% WG formulation specifies that the grazing of treated fields or feeding of treated forage or hay to livestock is prohibited. The label states that activity on emerged weeds requires the addition of an adjuvant (crop oil concentrate, methylated seed oil, or nonionic surfactant). Applications are to be made in a minimum of 10 gal/A for ground equipment or a minimum of 5 gal/A for aerial equipment.

The label indicates that the 85% WG formulation may be applied in a tank mix with one or more other herbicides. The most restrictive label for all products is to be followed. The following tank mix partners are identified: for corn, atrazine, Balance Pro® (isoxaflutole), Callisto® (mesotrione), Guardsman Max® (dimethenamid-P and atrazine), glyphosate, Outlook® (dimethenamid-P), and Python® (flumetsulam); and for soybean, Extreme® (imazethapyr and glyphosate), Gangster FR® (cloransulam-methyl), Gangster V® (flumioxazin), glyphosate, Lorox® (linuron), Outlook® (dimethenamid-P), Prowl® (pendimethalin), Pursuit® (imazethapyr), Python® (flumetsulam), Scepter® (imazaquin), Valor SX® (flumioxazin), and Valor XLT® (flumioxazin and chlorimuron ethyl). For wheat, the label for the 85% WG formulation specifies that the product may be tank mixed with herbicides registered for use on fall and winter wheat.

The label for the 42.5% WG formulation specifies that the product may be tank mixed with the following herbicides for application to soybean: 2,4-D, Command® (clomazone), Extreme® (imazethapyr and glyphosate), Firstrate® (cloransulaM-methyl), glyphosate, Lorox® (linuron), metribuzin, paraquat, pendimethalin, Pursuit Plus® (imazethapyr and pendimethalin), Python® (flumetsulam), Scepter® (imazaquin), Select® Max (clethodim), and Weedmaster® (dicamba and 2,4-D). The product may be tank mixed with glyphosate and/or dicamba for application to field corn.

A 12-hour restricted entry interval is specified.

The 42.5% WG formulation includes use directions for applications to fallow land and non-crop areas of farms, orchards, and vineyards, at 0.16-0.27 lb ai/A.

The following rotational crop restrictions have been proposed for the 85% WG formulation: a 0-day PBI for any crop on the label, with a prohibition against a second application of pyroxasulfone; and an 18-month PBI for crops other than corn, soybean, and wheat.

For the 42.5% WG formulation, the proposed rotational crop restrictions are dependent on application rates. For applications at up to 0.12 lb ai/A, a 0-day PBI is proposed for soybeans; a 14-day PBI is proposed for minimum or no-till field corn; a 30-day PBI is proposed for conventionally tilled field corn; and an 18-month PBI is proposed for all other crops. For applications at up to 0.16 lb ai/A, a 4-month PBI is proposed for soybeans and field corn and an

18-month PBI is proposed for all other crops. For applications at up to 0.27 lb ai/A, a 6-month PBI is proposed for soybeans and field corn and an 18-month PBI is proposed for all other crops. We note that applications at 0.16 or 0.27 lb ai/A may only be made to fallow land or non-crop areas.

Conclusions. The use directions are adequate to allow evaluation of the residue data relative to the proposed use in the U.S. The proposed maximum seasonal rates are generally supported by the submitted field trial data. HED has determined that the proposed PHIs and PGIs for corn and soybean commodities are not necessary. Label amendments are required to remove the proposed PHIs and PGIs and to modify the proposed maximum seasonal rates for some soil types.

The proposed uses on field corn, sweet corn, and soybean are all restricted to crop growth stages: for field and sweet corn, application is to be made up to the V4 growth stage; for soybean, application is to be made up the third trifoliate leaf growth stage; and for wheat, application is to be made preemergence. Because applications are based on defined growth stages, and crop commodities were harvested at appropriate crop growth stages in the field trials submitted with this petition, no PHIs or PGIs need to be specified for any field corn, sweet corn, or soybean commodity. Therefore, the product label for the 85% WG formulation should be amended to remove the following: the 37-day PHI for sweet corn ears; the 7-day PGI for corn and corn forage; the 15-day PHI for soybeans; and the 7-day PGI for soybean and soybean forage, hay, and straw.

For wheat, the proposed use is also restricted to crop growth stage (preemergence). However, in the crop field trials submitted with this petition, wheat forage was harvested at various intervals, at unspecified crop growth stages. The tolerance calculation for wheat forage was based on residue data reflecting PHIs of ≥40 days; therefore, the proposed PGI of 42 days is appropriate. When the required additional crop field trial data for wheat have been submitted, HED may determine that a PGI is no longer needed for wheat.

The available field trial data for field and sweet corn reflect a single postemergence application at 0.268 lb ai/A for fine- and medium-textured soils or at 0.148 lb ai/A for coarse-textured soils. The petitioner must amend the product label for the 85% WG formulation to specify a maximum seasonal rate of 0.268 lb ai/A for field and sweet corn grown in fine-, medium-fine-, and medium-textured soils, and a maximum seasonal rate of 0.148 lb ai/A for field and sweet corn grown in coarse-textured soils.

The product label for the 42.5% WG formulation must be amended to specify a maximum seasonal rate for field corn. Because application rates on this product are not dependent on soil type, the proposed maximum seasonal rate must be ≤0.148 lb ai/A.

The available field trial data for soybean reflect a single postemergence application at 0.186 lb ai/A for fine- and medium-textured soils or at 0.112 lb ai/A for coarse-textured soils. Insufficient field trial data were submitted to support single application rates greater than 0.186 lb ai/A. The petitioner must amend the product label for the 85% WG formulation to specify a maximum single and seasonal application rate of 0.186 lb ai/A for soybean grown in fine-, medium-fine-, and medium-textured soils, and a maximum seasonal rate of 0.112 lb ai/A for soybean grown in coarse-textured soils.

Based on the use pattern information included with the OECD dossier submission for the 85% WG formulation, the petitioner intends that only one application be made in the spring to corn, soybean, and wheat. For corn and soybean, for which two applications may be made, the petitioner intends that the split application be made as one application in the fall before planting and one application in the spring. The petitioner must amend the product label to specify that no more than one application may be made in the spring.

The product label for the 85% WG formulation must be amended to specify a maximum seasonal application rate to wheat of 0.11 lb ai/A.

The label for the 42.5% WG formulation states that activity on emerged weeds requires the addition of an adjuvant. No residue data have been submitted to support the use of an adjuvant with application of the product. The statement about adjuvant use must be removed from the product label.

For the 42.5% WG formulation, the petitioner must remove Weedmaster® from the list of tank mix partners for application to soybean, as this product (EPA Reg. No. 7969-133) is not registered for use on soybeans. The petitioner should also amend the label to specify that when the product is to be applied in a tank mix, the most restrictive label of all products used must be followed.

The 42.5% WG formulation, which is only proposed for application to field corn and soybeans, includes a restriction against the grazing of treated fields or feeding of treated forage or hay to livestock. HED does not believe that a restriction against the grazing or feeding of treated field corn forage or stover is practical; therefore, the restriction must be amended to state that the restriction only applies to soybeans.

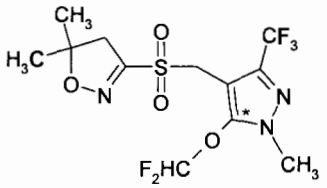
The proposed rotational crop restrictions for the 85% WG and 42.5% WG formulations are not supported by the available rotational crop data (see 860.1850 and 860.1900); additional data are required to determine whether rotational crop tolerances are needed to support the proposed 18-month PBI for crops not on the label. Until the required rotational crop data have been submitted, the petitioner must modify the labels for both products to specify that only root crops and crops on the label may be planted after pyroxasulfone application; crops on the label may be planted any time after application, and root crops may be planted 12 months after application.

860.1300 Nature of the Residue - Plants

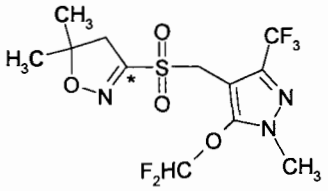
Monograph for Pyroxasulfone, Sections B.7.1.1 and B.7.1.2 (MRIDs 47701649 and 47701650)

The petitioner submitted studies pertaining to the metabolism of pyroxasulfone in corn and soybean. Two different radiolabels were used in the plant studies; the label positions are presented below:

[pyrazole-5-^{14}C]pyroxasulfone



[isoxazoline-3-^{14}C]pyroxasulfone



A number of metabolites were identified in these studies. The chemical structures and report names for these metabolites are provided in Appendix I.

Field corn (MRID 47701649): The metabolism of pyroxasulfone was investigated in field corn following a single application of [^{14}C]pyroxasulfone (pyrazole or isoxazoline labeled), formulated as a WG formulation in water, at a rate of approximately 1500 g ai/ha (1.34 lb ai/A; ~5x the proposed maximum seasonal rate). Application was made preemergence or early postemergence (growth stage V4) in an application volume of 500 or 822 L/ha (53 or 88 gal/A), respectively.

Total radioactive residues (TRR) were 2.717, 1.132, 3.485, and 2.474 ppm in corn foliage harvested at BBCH 34 (forage stage), 53 (tassel emergence stage), 79 (mid-fruit development stage), and 99 (maturity), respectively; and 0.073 and 0.132 ppm in corn grain (kernels) harvested at BBCH 79 and 99, respectively, following preemergence application of [pyrazole-5-^{14}C]pyroxasulfone. TRR were 2.213, 1.444, 1.771, and 3.250 ppm in corn foliage harvested at BBCH 34, 53, 79, and 99, respectively; and 0.034 and 0.101 ppm in corn grain harvested at BBCH 79 and 99, respectively, following preemergence application of [isoxazoline-3-^{14}C]pyroxasulfone.

Following postemergence applications with [pyrazole-5-^{14}C]pyroxasulfone, TRR were 1.905, 5.118, and 3.315 ppm in corn foliage harvested at BBCH 53, 79, and 99, respectively; and 0.007 and 0.024 ppm in corn grain harvested at BBCH 79 and 99, respectively. TRR were 4.861, 4.121, and 2.894 ppm in corn foliage harvested at BBCH 53, 79, and 99, respectively; and 0.026 and 0.048 ppm in corn grain harvested at BBCH 79 and 99, respectively, following postemergence application of [isoxazoline-3-^{14}C]pyroxasulfone.

TRR levels in the foliage treated postemergence were higher than those observed in the samples from preemergence treatment for both labels. TRR in grain were lower in samples treated postemergence than in samples treated preemergence.

Surface wash with acetonitrile (ACN) removed a greater proportion of the foliage residues from the samples treated postemergence (up to 40% TRR) than from the foliage samples treated preemergence (up to 7%); <1% of the TRR was removed from grain with the surface rinse. The majority of the remaining TRR was removed with acetone/water extractions, with levels of recovered radioactivity ranging 52-94% TRR in foliage and 58-70% TRR in grain (preemergence treatment only); no radioactivity was extracted from grain treated postemergence. Further extraction of foliage samples with water, 0.1 M hydrochloric acid and sodium hydroxide, 2 M hydrochloric acid and sodium hydroxide, and acetone individually recovered further levels of TRR up to 6% TRR. Only 2 M acid/base hydrolysis released additional radioactivity (3-11%

TRR) from mature grain treated preemergence. Levels of unextracted residue ranged 0.5-24% TRR (0.014-0.973 ppm) in the foliage and 29-100% TRR (0.007-0.048 ppm) in the grain; unextracted residues were <10% TRR or <0.05 ppm in all matrices, with the exception of foliage harvested at BBCH 79.

Only the mature samples were analyzed for metabolite characterization/identification. Metabolites were identified by high performance liquid chromatography (HPLC) and thin layer chromatography (TLC) co-chromatography. HPLC isolation followed by LC/MS analysis was used in an attempt to elucidate the potential structures of the unknowns that formed the major part of the residue.

No pyroxasulfone was found in mature foliage (stover) following preemergence application; the metabolites M-1 (37% TRR; 0.91 ppm), M-25 (27% TRR; 0.68 ppm), and M-29 (16% TRR; 0.50 ppm) were major contributors to the residue. The majority of the residue in stover was in the form of parent pyroxasulfone (23-33% TRR; 0.77-0.95 ppm) and its metabolites M-1 (23% TRR; 0.77 ppm) and M-25 (24% TRR; 0.79 ppm) following postemergence application. The metabolites M-3, M-6, M-8, M-9, and M-10 were identified as minor residues in stover following preemergence treatment, each at <4% TRR (<0.08 ppm); and metabolites M-1, M-6, M-9, and M-29 were identified as minor residues in stover treated postemergence, each at <10% TRR (<0.30 ppm). Approximately 73-76% TRR was identified in stover treated with [pyrazole-5-^{14}C]pyroxasulfone and 16-43% TRR was identified in stover treated with [isoxazoline-3-^{14}C]pyroxasulfone.

Pyroxasulfone was not detected in grain following preemergence application. Because radioactivity could not be extracted from postemergence application grain, the nature of the residues could not be characterized. The metabolites M-1, M-3, M-25, and M-29 were components of the grain residues; however, their levels in grain (each ≤5% TRR, ≤0.006 ppm) were much lower than in stover. Approximately 30% TRR was identified in grain treated with [pyrazole-5-^{14}C]pyroxasulfone and 1.1% TRR was identified in grain treated with [isoxazoline-3-^{14}C]pyroxasulfone.

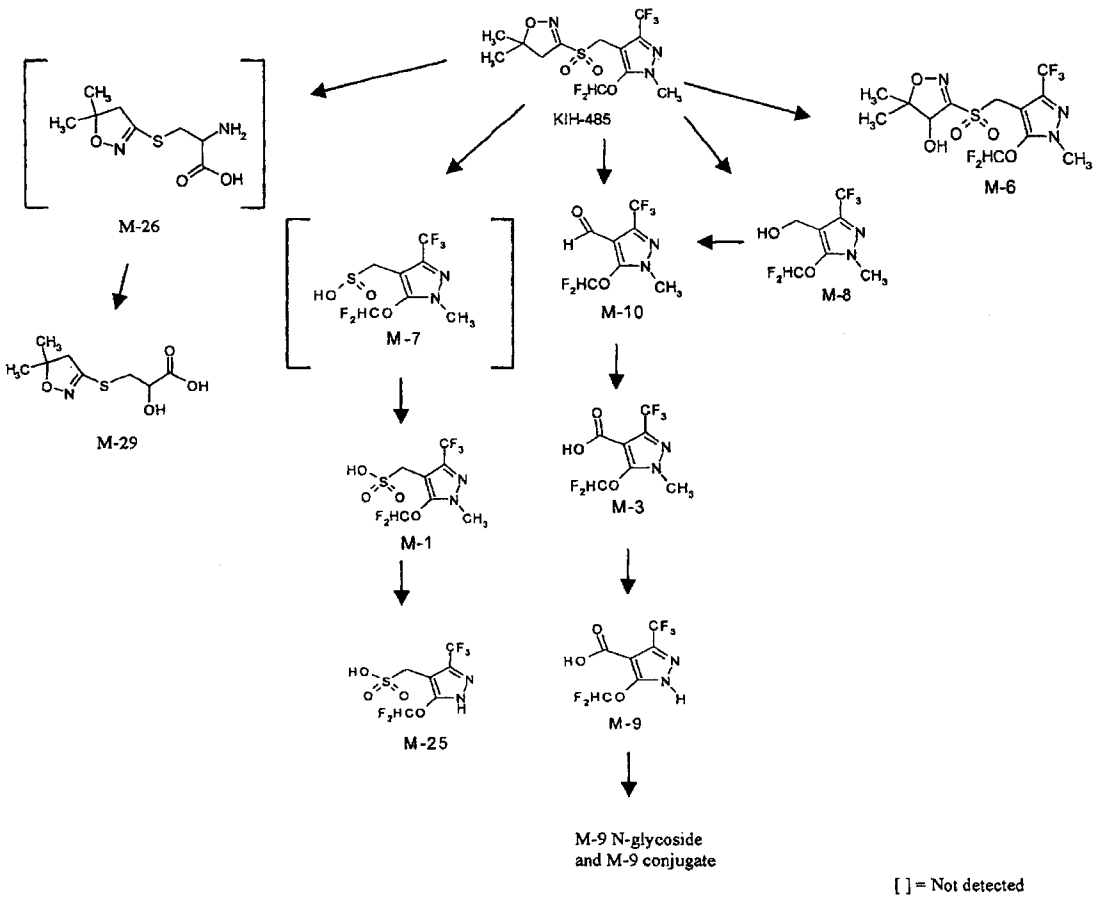
Unidentified minor metabolites in stover and grain were not considered to be significant (each ≤9.5% TRR, with the exception of one unknown in stover, which was found at 13.7% TRR, 0.446 ppm). One unknown found in stover at 4-5% TRR (0.11-0.13 ppm) and in grain at 19% TRR (0.025 ppm) was tentatively identified as the N-glycoside of M-9. Another unknown found in stover at 3-4% TRR (0.08-0.13 ppm) was characterized as a conjugate of M-9.

The petitioner proposed that pyroxasulfone is metabolized in corn via cleavage of the methyl sulfone bridge of the parent, forming an intermediate metabolite (M-7, which was not found in corn matrices) which undergoes oxidation to form the sulfonic acid metabolite M-1. Metabolite M-25 is formed following demethylation of M-1. For the other pyrazole-ring metabolites, the carboxylic acid metabolite M-3 likely forms from metabolites M-8 and M-10, with subsequent demethylation to form M-9, which may be further conjugated. In the case of the isoxazoline-ring metabolites, an intermediate cysteine conjugate (M-26, which was not found) may form from pyroxasulfone; subsequent deamination of M-26 would result in the formation of the conjugate M-29.

HED notes that the petitioner additionally characterized/identified radioactivity in samples of corn root; these data are not discussed here. No unique metabolites were found in roots.

The initial analyses of the treated acetone/water, acid and base extracts and the unretained material were completed within six months of harvest. Analysis of the confirmatory extracts by HPLC was not completed within six months of harvest but the profiles confirmed the results from the initial analysis.

Postulated pathways of formation of metabolites identified in field corn following pre-emergence and post-emergence treatment with KIH-485



Soybean (MRID 47701650): The metabolism of pyroxasulfone was investigated in soybean following a single application of [^{14}C]pyroxasulfone (pyrazole or isoxazoline labeled), formulated as a WG formulation, in water at a rate of 0.535 lb ai/A (~600 g ai/ha) preemergence (2.5x the proposed maximum preemergence application rate of 0.21 lb ai/A) or 0.373 lb ai/A (~418 g ai/ha) postemergence (2x the proposed maximum postemergence application rate of 0.19 lb ai/A), in an application volume of 500 or 700 L/ha (53 or 75 gal/A), respectively.

TRR were 1.339, 2.175, 0.496, and 3.796 ppm in soybean foliage harvested at BBCH 49 (forage stage), 61 (first-flower opening stage), 75 (mid-fruit/seed development stage), and 99 (maturity), respectively; and 0.015 and 0.312 ppm in soybean seed harvested at BBCH 75 and 99, respectively, following preemergence application of [pyrazole-5-^{14}C]pyroxasulfone. TRR were 3.700, 1.142, 0.498, and 3.347 ppm in soybean foliage harvested at BBCH 49, 61, 75, and 99, respectively; and 0.014 and 1.137 ppm in soybean seed harvested at BBCH 75 and 99, respectively, following preemergence application of [isoxazoline-3-^{14}C]pyroxasulfone.

Following postemergence application of [pyrazole-5-^{14}C]pyroxasulfone, TRR were 4.445, 1.517, and 5.671 ppm in soybean foliage harvested at BBCH 61, 75, and 99, respectively; and 0.011 and 1.267 ppm in soybean seed harvested at BBCH 75 and 99, respectively. TRR were 3.410, 1.468, and 6.945 ppm in soybean foliage harvested at BBCH 61, 75, and 99, respectively; and 0.016 and 1.362 ppm in soybean seed harvested at BBCH 75 and 99, respectively, following postemergence

application of [isoxazoline-3-^{14}C]pyroxasulfone. During the subsequent characterization and identification of the residues, it became evident that there had been a mix-up during the sampling procedures. In general, the composite samples from the postemergence treatment plots contained a mixture of plant material that had been treated with [pyrazole-5-^{14}C]pyroxasulfone and [isoxazoline-3-^{14}C]pyroxasulfone. However, for samples harvested at BBCH 75, the foliage and seed samples from both plots consisted solely of material that had been treated with [pyrazole-5-^{14}C]pyroxasulfone.

After preemergence treatment with the [pyrazole-5-^{14}C]-label or the [isoxazoline-3-^{14}C]-label, the TRR levels in the foliage and roots were a similar order of magnitude at each harvest, and showed little difference between the two radiolabelled forms of pyroxasulfone. Levels were low in the seeds at the mid-fruit/seed development harvest, but had increased considerably by the time maturity had been reached. The lowest TRR values in all matrices were obtained at the mid-fruit/seed harvest. This may be attributed to the poor health of the plants at this stage. Some evidence of phytotoxic effects was observed during the growth of the plants and, in order to ensure sufficient sample was available for the mature harvest, a decision was made to harvest the plants in the poorest state of health at the mid-fruit/seed harvest. The healthiest plants were sampled at maturity since these were used for profiling.

As a result of the sampling error, it was not possible to compare the distribution of radioactive residues between the two radiolabelled forms of pyroxasulfone in the postemergence crop fractions. Nevertheless, the TRR levels observed at each harvest interval, following application to postemergence plants, were of a similar order of magnitude to those following preemergence application.

Surface washes with ACN removed up to 15% TRR from foliage; no radioactivity was removed from seeds with the surface rinse. The majority of the remaining TRR was removed with acetone/water and water extractions, with levels of recovered radioactivity ranging 66-84% TRR in foliage, and 85-91% TRR in mature seed; no radioactivity was extracted from seed collected at the mid-fruit/seed development stage (BBCH 75). Further extraction of the mature samples with 0.1 M hydrochloric acid and sodium hydroxide, 2 M hydrochloric acid and sodium hydroxide, and acetone individually recovered further levels of TRR up to 13% TRR. Levels of unextracted residue ranged 13-26% TRR (0.092-0.811 ppm) in immature foliage, 9-14% TRR (0.325-1.000 ppm) in mature foliage, and 3-7% TRR (0.021-0.049 ppm) in mature seeds. In the postemergence foliage samples, there appeared to be a decrease in the %TRR extracted with acetone/water as the samples matured. This differs from the preemergence foliage samples where a decrease in extractability with acetone/water was not clearly evident. Mature seed samples had the highest extractability.

Metabolites were identified by HPLC and TLC co-chromatography. HPLC isolation followed by LC/MS was used in an attempt to elucidate the accurate masses and potential structures of the unknowns that formed the major part of the residue.

Foliage collected at the first flower harvest (BBCH 61) is considered to be representative of soybean forage, and although foliage collected at the mid-fruit harvest (BBCH 75) was not dried, it was collected when soybean hay is typically harvested. No pyroxasulfone was identified in first-flower harvest foliage, and only small amounts (≤1% TRR) of pyroxasulfone were identified

in mid-fruit harvest foliage. The major residues identified in both first-flower and mid-fruit harvest foliage were M-1, M-25, and M-28 following pre- and postemergence application. Metabolites M-1, M-25, and M-28 accounted for 5.7-14% (0.20-0.30 ppm), 5.1-13% (0.17-0.27 ppm), and 38-55% TRR (0.63-2.46 ppm), respectively, in first flower harvest foliage, and 13-16% (0.07-0.20 ppm), 6.8-12% (0.055-0.17 ppm), and 35% TRR (0.17 ppm), respectively, in mid-fruit harvest foliage. An unknown tentatively characterized as a possible conjugate of M-9 was the major residue detected in first flower harvest foliage following preemergence application accounting for 34% TRR (0.75 ppm) and in mid-fruit harvest foliage accounting for 20-31% TRR (0.15-0.30 ppm); this metabolite was a minor residue (~8% TRR, 0.26 ppm) in first flower harvest foliage following postemergence application. Approximately 35-61% TRR was identified in BBCH 61 and 75 foliage. HED notes that because samples harvested at BBCH 75 from both plots consisted solely of material that had been treated with [pyrazole-5-^{14}C] pyroxasulfone, there was no sample available of mid-fruit harvest foliage treated with [isoxazoline-3-^{14}C]pyroxasulfone.

Limited amounts of pyroxasulfone (≤1.6% TRR, ≤0.11 ppm) were present in mature foliage and seeds following pre- and postemergence application. In the mature foliage, M-1 was the main metabolite accounting for up to 32% TRR (up to 1.2 ppm) while M-25 was a minor metabolite (<7% TRR, ≤0.26 ppm). M-1 and M-25 were not detected in the seeds. The conjugate M-28 was a major metabolite in mature foliage (≤33.2% TRR, ≤1.49 ppm) and mature seeds (≤52.0% TRR, ≤0.65 ppm), following pre- and postemergence application. The conjugate M-29 (co-eluting with M-1) was also considered a major metabolite, accounting for up to 13.5% TRR (0.94 ppm) in mature foliage. Other metabolites were formed but comprised only a small proportion of the residue; those metabolites which were unable to be identified were each present at ≤7.8% TRR. Approximately 34-64% TRR was identified in mature foliage and 43-52% TRR was identified in seed, except seed treated preemergence with [pyrazole-5-^{14}C]pyroxasulfone, in which only 5.5% TRR was identified.

The petitioner proposed that pyroxasulfone is metabolized in soybean via cleavage of the methyl sulfone bridge of the parent, forming an intermediate metabolite (M-7, which was not found in soybean matrices) which undergoes oxidation to form the sulfonic acid metabolite M-1. Metabolite M-25 is formed following demethylation of M-1. For the other pyrazole-ring metabolites, the carboxylic acid metabolite M-3 likely forms from metabolites M-8 and M-10, with subsequent demethylation to form M-9, which may be further conjugated. In the case of the isoxazoline-ring metabolites, an intermediate cysteine conjugate (M-26, which was not found) may form from pyroxasulfone; subsequent deamination of M-26 would result in the formation of the conjugate M-29. Malonylation of M-26 results in the formation of malonyl-cysteine conjugate M-28.

HED notes that the petitioner additionally characterized/identified radioactivity in samples of soybean root; these data are not discussed here. Two metabolites were identified in roots that were not identified in foliage or seeds, M-8 and M-10 (each at <2% TRR).

Samples were stored frozen prior to analysis but no dates of extraction and/or analysis were provided for any sample. Based on the sample harvest dates and the reported date of completion of metabolite identification, samples may have been stored for up to 23 months prior to completion of analysis. The petitioner stated that because initial analyses of the treated samples

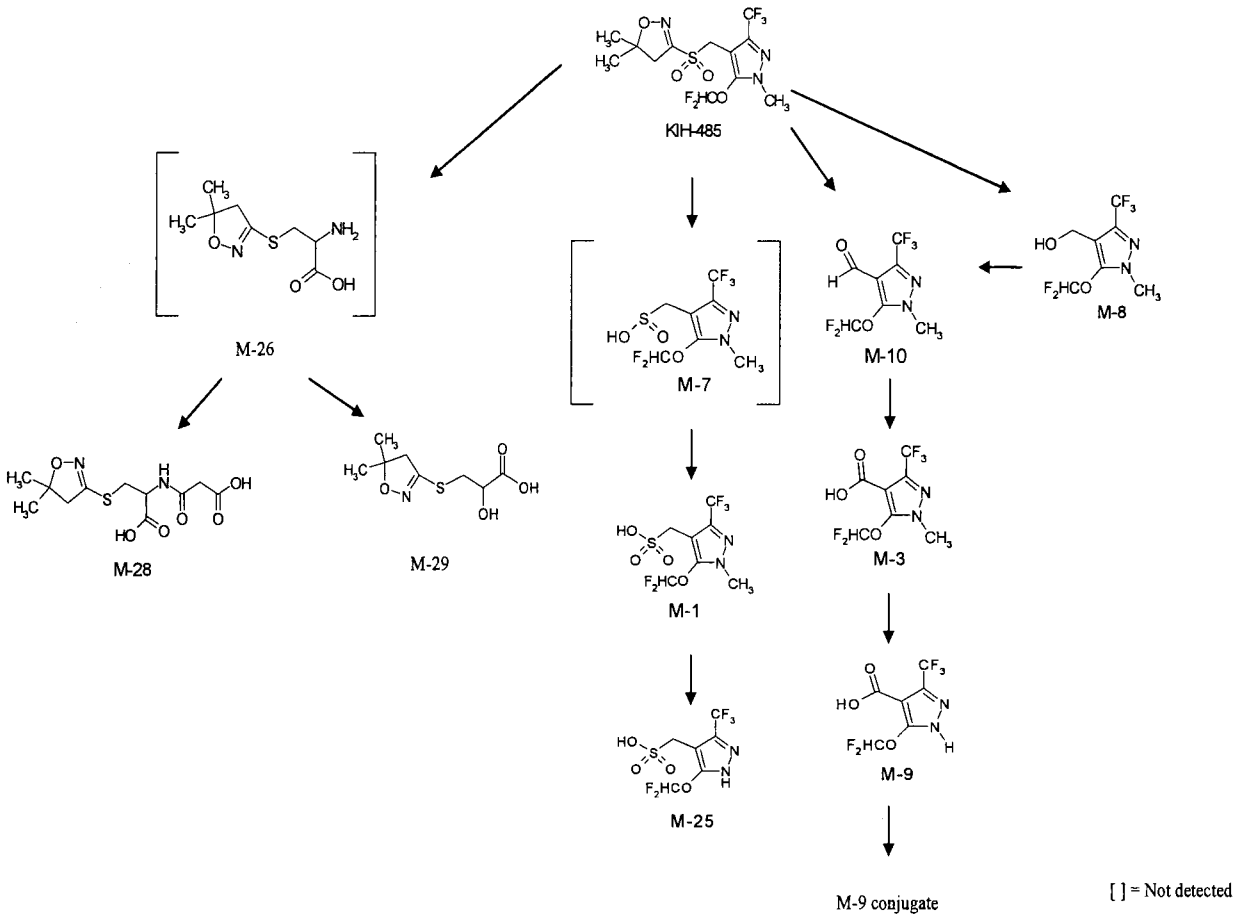
were not completed within three months of harvest, sub-samples of the mature foliage (pre-and postemergence) were re-extracted and analyzed; comparison of the HPLC profiles to the original data reportedly confirmed the stability of the samples during frozen storage. No data were provided to support these statements, including any indication of the length of time between the initial analyses and the repeat analyses.

Conclusions. The submitted data are partially adequate to satisfy data requirements. Although the petitioner harvested and extracted immature corn samples, the petitioner did not identify/characterize radioactivity in corn forage, a major raw agricultural commodity (RAC) of corn. Normally data on corn forage would be required. However, the petitioner did identify a high percentage of radioactivity in corn stover. Therefore, metabolism data on corn forage will not be required.

For the soybean study, residues in the immature commodities soybean forage (foliage collected at first flower) and hay (foliage collected at mid-fruit) were not sufficiently characterized/identified. Nonextractable residues in these commodities were 13-26% TRR (0.092-0.811 ppm). Additional attempts should be made to release radioactivity, such that nonextractable residues are <10% TRR or <0.05 ppm. In addition, the petitioner must provide additional information pertaining to storage stability. The dates of sample extraction and analysis should be provided for all samples, including the samples that were re-extracted for storage stability confirmation. These data will allow HED to determine whether the data are sufficient to demonstrate that the identity of residues did not change during the period between collection and final analysis. In addition, supporting storage stability data will be needed for the required additional analyses for immature foliage matrices.

Due to a sampling mix-up, no samples were available of soybean hay from plots treated with [isoxazoline-3-^{14}C] pyroxasulfone. Based on the sample used in the radiovalidation study (MRID 47701665), the petitioner appears to have initiated another soybean metabolism study. When the required additional data described above and/or the new soybean metabolism study have been submitted and evaluated, HED will determine whether any additional data for soybean hay treated with [isoxazoline-3-^{14}C] pyroxasulfone are needed.

Postulated pathways of formation of metabolites identified in soybean following pre-emergence and post-emergence treatment with KIH-485



Pending submission of the additional crop metabolism data, HED (G. Kramer, 7/30/2010, D379930) has concluded that, for the purposes of this petition, the residues of concern for risk assessment and tolerance enforcement in cereal grains consist of pyroxasulfone and its metabolites M-1, M-3, and M-25. Residues of concern for tolerance enforcement in soybeans consist of pyroxasulfone and its metabolites M-1, M-3, and M-25. However, residues of concern for risk assessment in soybeans consist of pyroxasulfone and its metabolites M-1, M-3, M-25, and M-28. After reanalysis of soybean seed samples for M-28, this metabolite may need to be added as a residue of concern in tolerance enforcement for soybean.

860.1300 Nature of the Residue - Livestock

Monograph for Pyroxasulfone, Sections B.7.2.1 and B.7.2.2 (MRIDs 47701651-47701655)

There are several livestock feedstuffs associated with the proposed uses of pyroxasulfone. The petitioner provided livestock metabolism studies with lactating goats and laying hens, which are summarized below.

Hen

MRID 47701651: The absorption, distribution and excretion of [^{14}C] pyroxasulfone were investigated following repeated oral administration to the laying hen. [Pyrazole-^{14}C]Pyroxasulfone was orally administered daily to five laying hens at a nominal dose level of 10 ppm in the diet for 10 consecutive days. Excreta were collected daily and eggs collected twice daily. Approximately 23 hours following the final dose administration, the hens were sacrificed, and liver, skin, muscle and fat were either excised or sampled as appropriate. Radioactivity was determined in all samples by direct liquid scintillation counting (LSC) or LSC following solubilization.

The actual mean dose was 2.129 mg/animal/day, equivalent to 14.8 ppm in the diet, which is ~780x the estimated dietary burden to poultry (see Table 6). The mean recovery of radioactivity was 88% of the administered dose; 86% of the administered dose was excreted.

Radioactivity was detected in egg yolks, at 0.0494-0.1281 ppm, and egg whites, at 0.0250-0.0798 ppm, at all time points. Steady-state conditions were achieved within 3 days of the first dose in egg white and within 10 days in egg yolk. Radioactivity was detected in all tissues; concentrations were 0.4973 ppm in liver, 0.1054 ppm in muscle, 0.0492 ppm in skin and 0.0216 ppm in fat. Concentrations of radioactivity were 0.1113 ppm in blood and 0.0578 ppm in plasma.

Residues in egg white and egg yolk were relatively extractable with organic solvents [hexane, ethyl acetate (EtOAc), ACN, acidified ACN, and methanol], at 90% and 57% TRR, respectively; protease digestion and 6 M acid hydrolysis released an additional 15% and 18% TRR from egg yolk. Residues in the tissues were not easily extractable with either organic (hexane, EtOAc, ACN, acidified ACN, and methanol) or more polar solvents (water, 1 M HCl, and 1M NH_3), which extracted 32-40% TRR in total from each matrix. The residues were mostly released following protease digestion (32-51% TRR) or vigorous acidic hydrolysis (19-27% TRR). The petitioner concluded that the more aggressive extraction methods may have converted the residues to different components which may or may not have been present in the original sample. Nonextractable residues after exhaustive extraction were <10% TRR or <0.05 ppm in all matrices.

Extracts were analyzed by HPLC, and proposed identities were assigned to the putative residues based solely on the chromatographic retention times.

Approximately 3-28% TRR was identified in egg and tissues. There were two identifiable metabolites which exceeded a concentration of 0.01 ppm in any matrix which were M-1, at 0.039 ppm (7.8% TRR) in liver, and M-12, at 0.0130 ppm (2.6% TRR) in liver and 0.0114 ppm (9.5% TRR) in egg yolk. There was only one identifiable metabolite which exceeded 10% of the total radioactive residue for any matrix, M-12 at 11% TRR (0.0030 ppm) in egg white.

A peak with similar chromatographic properties to pyroxasulfone was found only in egg yolk, fat and skin, at less than 0.002 ppm (0.8-3.3% TRR). Many of the residues showed similar chromatographic properties to supplied metabolite standards, namely M-1, M-3, M-5, M-6, M-8, M-9, M-10, M-11, M-12 and M-13. The metabolites identified in egg white were M-12, M-5, and M-6, each at <12% TRR (<0.004 ppm), and the metabolites identified in egg yolk were M-1, M-12, M-5, M-6, M-8, M-9, M-10, and pyroxasulfone, each at <10% TRR (<0.012 ppm).

Metabolites identified in muscle were M-1, M-10 and M-3 (0.1-3.0% TRR, each <0.004 ppm); in fat were M-12 and pyroxasulfone (each <4% TRR, ≤0.0008 ppm); and in skin were M-3, M-12, M-11, M-13, M-5 and pyroxasulfone (0.4-4.9% TRR, each <0.005 ppm). Analysis of liver showed M-1, M-8, M-3, and M-9 and/or M-12 (a residue tentatively identified as M-12 could be either M-9 or M-12), each at <8% TRR (<0.04 ppm).

The remaining residues in analyzed extracts consisted of unidentified peaks, none of which accounted for greater than 0.037 ppm in an individual matrix.

Samples were stored frozen prior to analysis but no dates of extraction and/or analysis were provided for any sample. Based on the reported dates of first dosing and completion of the experimental phase, final sample analysis may have been completed within 5.5 months of sample collection.

Based on the observed metabolites, the petitioner proposed that pyroxasulfone is metabolized in hens via cleavage between the rings to form metabolites M-1, M-8, and M-10. Oxidation of M-10 would yield metabolite M-3, and metabolites M-12 and M-9 could be formed via demethylation of M-8 and M-3, respectively. Hydroxylation of pyroxasulfone would yield metabolites M-6 and M-11, and further oxidation of M-11 would yield M-13. Metabolite M-5 could be formed via demethylation of pyroxasulfone.

MRID 47701652: The absorption, distribution and excretion of [isoxazoline-3-^{14}C] pyroxasulfone were investigated following repeated oral administration to the laying hen. The test substance was orally administered daily to five laying hens at a nominal dose level of 10 ppm in the diet for 3 consecutive days. Excreta were collected daily and eggs collected twice daily. Approximately 23 hours following the final dose administration, the hens were sacrificed, and liver, skin, muscle and fat were either excised or sampled as appropriate. Radioactivity was determined in all samples by direct LSC or LSC following solubilization.

The actual mean dose was 11.66 ppm in the diet, equivalent to ~610x the estimated dietary burden to poultry (see Table 6). The mean recovery of radioactivity was 103%; >99% of the administered dose was excreted.

Radioactivity was detected in egg yolks, at 0.0097-0.0976 ppm, and egg whites, at 0.0263-0.1080 ppm, at all time points. Radioactivity in egg whites may have reached a steady state by the end of the study; however, radioactivity in egg yolks appeared to be increasing at the end of the study. Radioactivity was detected in all tissues; concentrations were 0.1152 ppm in liver, 0.04081 ppm in muscle, 0.03265 ppm in skin and 0.008731 ppm in fat. Concentrations of radioactivity were 0.1918 ppm in blood and 0.0355 ppm in plasma. Due to low radioactivity levels, fat was not subjected to residue characterization.

Residues in egg white and egg yolk were relatively extractable with organic solvents (hexane, EtOAc, ACN, acidified ACN, and methanol), at 80% and 81% TRR, respectively. Residues in the tissues were not easily extractable with organic (EtOAc, ACN, acidified ACN, and methanol) or more polar solvents (water, 1 M HCl, and 1M NH_3), which extracted 18-46% TRR and 5-11% TRR, respectively. The residues were released only following protease digestion (18-28% TRR) or vigorous acidic or basic hydrolysis (9-26% TRR). The petitioner concluded that the more

aggressive extraction methods may have converted the residues to different components which may or may not have been present in the original sample. Nonextractable residues were <10% TRR or <0.05 ppm in all hen matrices following solvent and/or exhaustive extraction.

Extracts were analyzed by HPLC, and tentative identities of residues were assigned based solely on their chromatographic properties.

Very few of the residues showed similar chromatographic properties to supplied metabolite standards; only pyroxasulfone, M-5, M-11 and M-13 were tentatively identified. Pyroxasulfone was tentatively identified in liver (1.4% TRR, 0.0016 ppm), M-5 was tentatively identified in egg yolk (5.9% TRR, 0.0058 ppm), M-11 was tentatively identified in egg white and yolk (<1.5% TRR, <0.0015 ppm), and M-13 was tentatively identified in egg white, egg yolk, and skin (1.2-19.5% TRR, 0.0004-0.019 ppm). Only one identifiable metabolite exceeded a concentration of 0.01 ppm or a TRR of 10% in any matrix, which was M-13, at 19.5% TRR (0.0190 ppm) in egg yolk. Approximately 27% TRR was identified in egg yolk and <10% TRR was identified in egg white, liver, and skin; no metabolites were identified in muscle.

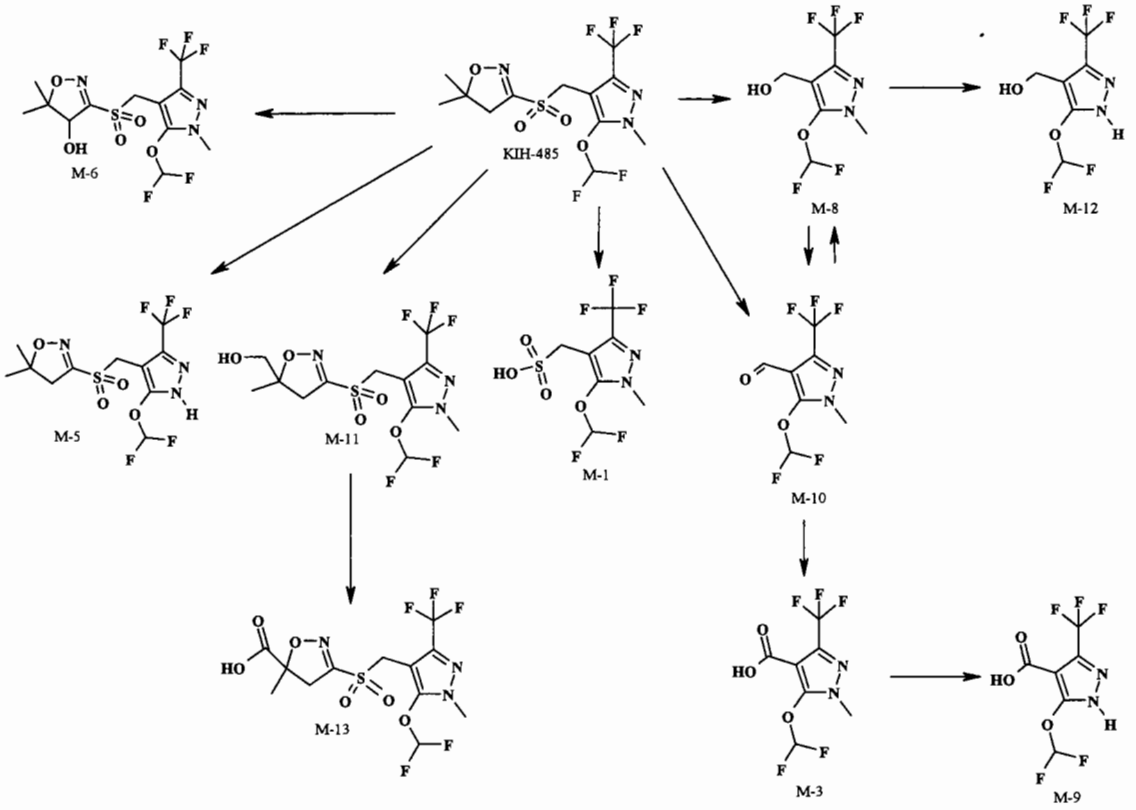
The remaining residues in analyzed extracts consisted of unidentified peaks, none of which accounted for greater than 0.031 ppm.

Samples were stored frozen prior to analysis but no dates of sample collection, extraction, or analysis were provided. The petitioner stated that the organic extracts from all samples were subjected to HPLC re-analysis following all metabolite profiling and that comparison of the data with the original analyses indicated stability of the residues during sample storage for the duration of the study. No data to support this statement were included in the submission. Based on the reported dates of first dosing and completion of the experimental phase, samples may have stored for up to 12 months prior to completion of analysis.

Based on the observed metabolites, the petitioner proposed that pyroxasulfone is metabolized in hens via demethylation to form metabolite M-5 or hydroxylation to form metabolite M-11; further oxidation of M-11 would yield M-13.

Conclusions. The submitted hen metabolism studies are adequate to satisfy data requirements for nature of the residue in poultry.

Proposed metabolite pathway of KIH-485 in laying hens following at a daily dose level of 2.129 mg/ animal/day [pyrazole-^{14}C]-KIH-485 (equivalent to 15 ppm in the diet) over 10 days



Goat

MRID 47701653: The absorption, distribution, metabolism and excretion of [^{14}C] pyroxasulfone were investigated following repeated oral administration to the lactating goat. [Pyrazole-^{14}C]Pyroxasulfone was orally administered daily to a lactating goat at a nominal dose level of 10 ppm in the diet for 5 consecutive days. Excreta were collected daily and milk collected twice daily. Approximately 23 hours following the final dose administration, the goat was sacrificed and liver, kidneys, muscle, and fat were either excised or sampled as appropriate. Radioactivity was determined in all samples by direct LSC or LSC following solubilization.

The actual dose was 11.89 ppm in the diet, equivalent to ~250x and 160x the estimated dietary burden to beef and dairy cattle, respectively (see Table 6). The recovery of radioactivity was 91.9% of the administered dose; the majority of radioactivity (84%) was excreted in the urine, with minimal amounts being recovered in the feces (4%).

Radioactivity was detected in milk at all time points: 0.0026-0.0042 ppm in morning samples and 0.0239-0.0297 ppm in afternoon samples. Steady-state conditions were achieved within two days of the first dose administration. Radioactivity levels in tissues were 0.2181 ppm in liver, 0.0171 ppm in kidneys, 0.0034 ppm in muscle, and 0.0015 ppm in omental fat. Radioactivity was below the limit of quantification in renal fat. Concentrations of radioactivity were 0.0052 ppm in blood and 0.0046 ppm in plasma.

Residues in milk (Day 5 pm sample), liver, and kidney were not readily extractable with organic solvents (hexane, EtOAc, ACN, acidified ACN, and/or methanol) or more polar solvents (water, 1 M HCl, and 1 M NH_3); 4-48% TRR was organosoluble and 5-7% TRR was aqueous soluble.

A large proportion of the residue was bound to endogenous materials and required more aggressive methods of extraction. The residues were mostly released following protease digestion (21-80% TRR), subsequent ACN extraction (2.5-12% TRR), or vigorous acidic hydrolysis (16-25% TRR). Nonextractable residues in milk, liver, and kidney after solvent extraction, protease digestion, and acid and base hydrolysis were <5% TRR. Due to low radioactivity levels, residues in muscle and fat were not subjected to residue characterization.

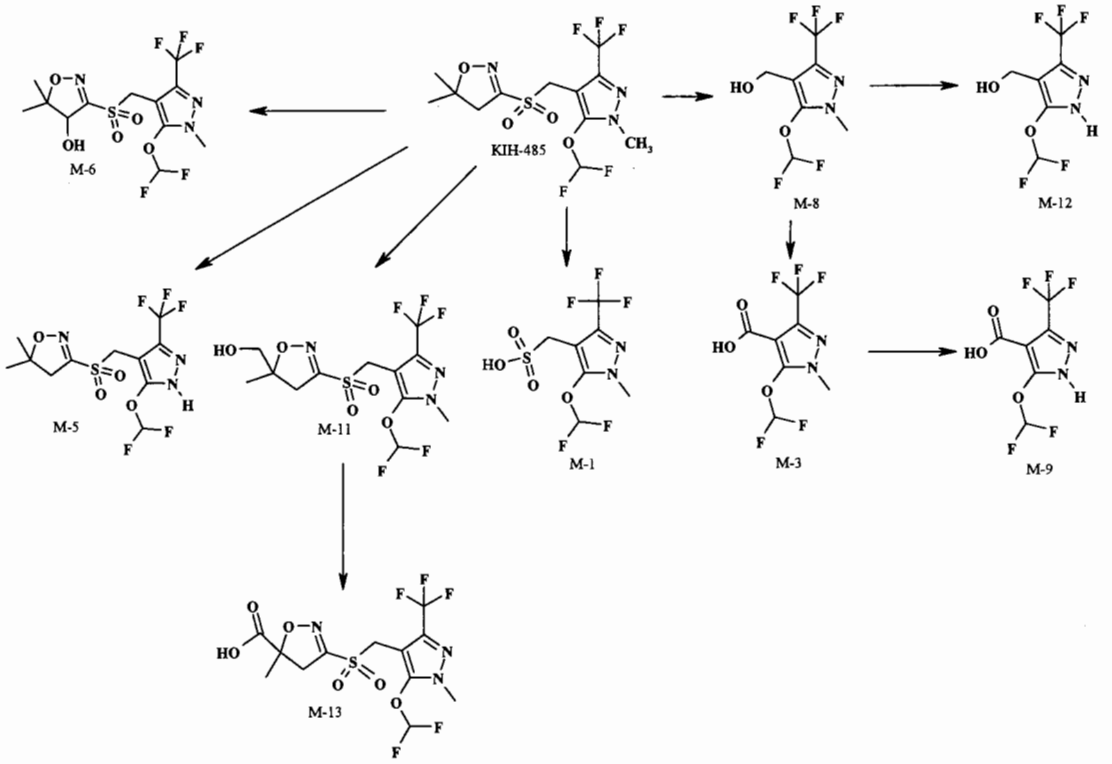
Extracts were analyzed by HPLC, and residues were tentatively identified based solely on their chromatographic properties.

Approximately 47%, 12%, and 23% TRR were identified in milk, liver, and kidney, respectively. Only one identifiable metabolite exceeded a concentration of 0.01 ppm in any matrix, M-12 at 0.0135 ppm (6.2% TRR) in liver. There was only one identifiable metabolite which exceeded 10% of the TRR for any matrix, M-13 at 25.2% TRR (0.0067 ppm) in milk.

In addition to M-13, the metabolites identified in milk were M-1, M-3, M-8, M-9, M-11, and M-12 (0.8-7.2% TRR, each <0.002 ppm). In addition to M-12, the metabolites identified in liver were M-1, M-3, M-5 and/or M-6, M-8, M-9, and M-11 (0.2-2.4% TRR, each <0.006 ppm). The metabolites identified in kidney were M-1, M-5 and/or M-6, M-8, and M-9 and/or M-12 (2.3-8.2% TRR, each <0.002 ppm). None of the residues released showed similar chromatographic properties to pyroxasulfone. The remaining residues in analyzed extracts consisted of unidentified peaks, none of which accounted for greater than 0.028 ppm.

Based on the observed metabolites, the petitioner proposed that pyroxasulfone is metabolized in goats via cleavage between the rings to form metabolites M-1 and M-8. Oxidation of M-8 would yield metabolite M-3, and metabolites M-12 and M-9 could be formed via demethylation of M-8 and M-3, respectively. Hydroxylation of pyroxasulfone would yield metabolites M-6 and M-11, and further oxidation of M-11 would yield M-13. Metabolite M-5 could be formed via demethylation of pyroxasulfone.

Proposed metabolite pathway in a lactating goat (n= 1) following oral administration of [^{14}C]-KIH-485 at a daily dose level of 19 mg/ animal/day (equivalent to 12 ppm in the diet) over 5 days



MRID 47701654: Because M-25 was identified as a major metabolite in the corn metabolism study, the petitioner examined goat urine, from the above metabolism study with [pyrazole-^{14}C] pyroxasulfone, for the presence of M-25 and other metabolites of pyroxasulfone.

Day-5 goat urine, and urine fortified with pyroxasulfone and reference standards, were analyzed by HPLC. There were up to 13 regions of interest in the profile of day-5 goat urine. Seven of the regions had similar chromatographic properties to the reference standards. The metabolites tentatively identified included M-25, accounting for 0.3%; M-1, accounting for 5.9%; M-12, accounting for 0.4%; M-7, accounting for 3.4%; M-8, accounting for 0.3%; M-3, accounting for 0.4%; and M-13, accounting for 3.2% of the administered dose.

MRID 47701655: The absorption, distribution, metabolism and excretion of [isoxazoline-3-^{14}C] pyroxasulfone were investigated following repeated oral administration to the lactating goat. The test substance was orally administered daily to a lactating goat at a nominal dose level of 10 ppm in the diet for 3 consecutive days. Excreta were collected daily and milk collected twice daily. Approximately 23.8 hours following the final dose administration, the goat was sacrificed and liver, kidneys, muscle, and fat were either excised or sampled as appropriate. Radioactivity was determined in all samples by direct LSC or LSC following solubilization.

The actual dose was 10.15 ppm in the diet, equivalent to ~210x and 140x the estimated dietary burden to beef and dairy cattle, respectively. The recovery of radioactivity was 82% of the administered dose. The majority of radioactivity was excreted in the urine (61%), with moderate amounts being recovered in the feces (11%).

Radioactivity was detected in milk at all time points: 0.0256-0.0335 ppm in morning samples and 0.0665-0.0912 ppm in afternoon samples. Steady-state conditions were not achieved during the study; the highest residues observed in milk were obtained on the last sampling day. Radioactivity was detected in all tissues; concentrations were 0.899 ppm in liver, 0.290 ppm in kidneys, 0.066 ppm in muscle, 0.040 ppm in renal fat and 0.039 ppm in omental fat. Concentrations of radioactivity were 0.291 ppm in blood and 0.362 ppm in plasma.

Residues in milk (Day 3 pm samples) and tissues were not readily extractable with organic solvents (hexane, EtOAc, ACN, acidified ACN, and/or methanol) or more polar solvents (water, 1 M HCl, and 1 M NH_3); 6-29% TRR was organosoluble and 5-7% TRR was aqueous soluble. The residues were mostly released following protease digestion (42-65% TRR), subsequent ACN extraction (4-23% TRR), or vigorous acidic hydrolysis (9-26% TRR). Nonextractable residues in milk and tissues after solvent extraction, protease digestion, and acid and base hydrolysis were <10% TRR or <0.05 ppm.

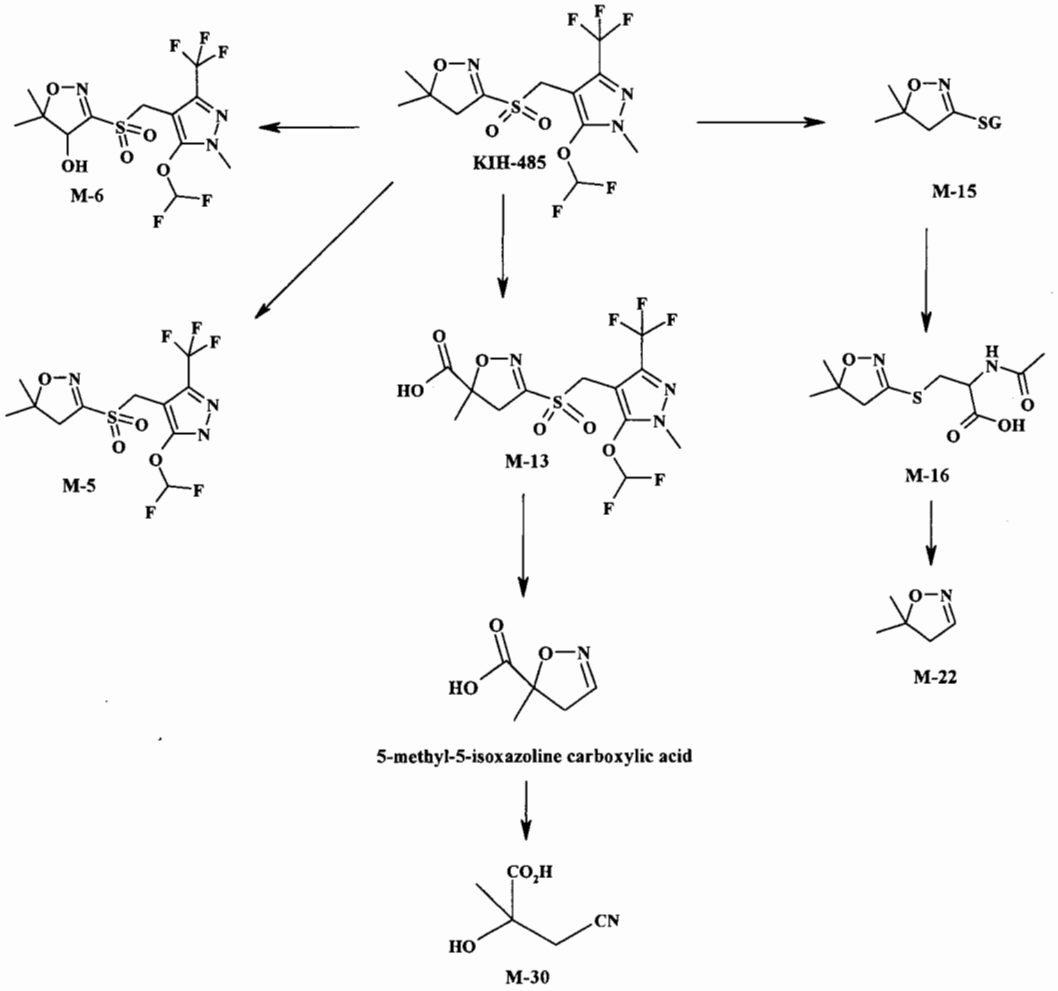
Extracts were analyzed by HPLC and residues were tentatively identified based solely on their chromatographic properties and co-chromatography with supplied metabolite standards. Further investigation of residues that were not retained on HPLC analysis and an unknown in the protease extract of liver was attempted using TLC and/or LC/MS; neither technique yielded additional metabolite identifications.

Many of the residues showed similar chromatographic properties to supplied metabolite standards, namely M-5, M-6, M-13, M-15, M-16, M-22 and pyroxasulfone, but each accounted for less than 0.014 ppm. Approximately 11% TRR was identified in milk and 1.3-3.1% TRR identified in liver, kidney, and muscle; no metabolites were identified in fat. No identified metabolite exceeded 10% of TRR in any matrix measured, and only one identified metabolite exceeded a concentration of 0.01 ppm, M-22 in liver at 0.0135 ppm (1.5% TRR). In addition to M-22, metabolites M-5, M-13, and M-16 were identified in liver (each <1% TRR, <0.007 ppm). Identified metabolites in milk were M-13, M-16, and M-22 (0.9-6.7% TRR, each <0.007 ppm); identified metabolites in kidney were M-6, M-15, M-22, and pyroxasulfone (each <1% TRR, <0.003 ppm); and only M-22 was identified in muscle (2.7% TRR, 0.0018 ppm).

Only residues which were not retained on the HPLC column individually accounted for greater than 0.050 ppm. TLC analysis of these un-retained residues did not yield any metabolite identifications. The petitioner stated that comparison of these results with results from a rat metabolism study (MRID 47701728; Covance Study Number 0535/138) indicated that the un-retained residues were multi-component and probably included metabolite M-30 and 5 methyl-5-isoxazoline carboxylic acid; however, limited data/discussion to support this statement were provided.

Based on the observed metabolites, the petitioner proposed that pyroxasulfone is metabolized in goats via oxidation, to form metabolite M-13, or hydroxylation, to form metabolite M-6. Cleavage of M-13 between the rings would yield 5-methyl-isoxazoline carboxylic acid, which may be further metabolized to M-30. Metabolite M-5 could be formed via demethylation of pyroxasulfone. Metabolite M-15 is formed via cleavage of pyroxasulfone, and further metabolism would yield metabolite M-16 and then M-22.

Proposed metabolite pathway in a lactating goat (n= 1) following oral administration of [^{14}C]-KIH-485 at a daily dose level of 13.6 mg/ animal/day (equivalent to 10 ppm in the diet) over 3 days



Samples were stored frozen prior to analysis but no dates of extraction and/or analysis were provided for any sample. The petitioner stated that the first organic extracts from all samples were re-subjected to HPLC analysis after all metabolite profiles had been determined and that comparison of the data indicated stability of the residues during sample storage for the duration of the study. No data to support this statement were included in the submission. Based on the reported dates of first dosing and completion of the experimental phase, samples may have stored for up to 12 months prior to completion of analysis.

Conclusions. The submitted goat metabolism studies are adequate to satisfy data requirements for nature of the residue in ruminants. Initially, for the study conducted with [isoxazoline-3-^{14}C] pyroxasulfone, the petitioner was required to provide additional discussion and supporting data for their statements that un-retained radioactivity accounting for >0.05 ppm was likely

multicomponent and contained M-30 and 5-methyl-5-isoxazoline carboxylic acid. The petitioner was required to explain why a reference standard for potential metabolite M-30 was not used in this study (an M-30 reference standard was used in the analogous hen metabolism study). The petitioner was also required to provide further explanation (and supporting data if available) of the attempts to identify residues by LC/MS.

No dates of sample collection, extraction, or analysis were provided. The petitioner was required to submit dates of collection, extraction, and analysis for each sample from all of the submitted studies. For the hen and goat studies reflecting pyrazole labeling (MRIDs 47701651 and 47701653), if the required data indicated that final sample analysis was not completed within 6 months of sample collection, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. For the hen and goat studies reflecting isoxazoline labeling (MRIDs 47701652 and 47701655), the petitioner was required to provide the comparative chromatographic data that were cited in the studies.

The petitioner has submitted theses outstanding data and these data were found to be acceptable (T. Morton, D395720, 11/17/11).

Based on the results of the goat and hen metabolism studies, HED has concluded that the residues of concern for tolerance enforcement in livestock commodities consist of pyroxasulfone and its metabolites M-1 and M-3. Residues of concern for risk assessment in livestock commodities consist of pyroxasulfone and its metabolites M-1, M-3, M-25, and M-28.

860.1340 Residue Analytical Methods

A summary of the analytical methods associated with this petition is presented in Table 4.

Table 4. Summary of Residue Analytical Methods.			
Matrix	Analytes	Method	Limit of quantitation (ppm)
Crop commodity enforcement method + independent laboratory validation			
Corn forage, grain, stover, grits, starch, meal, flour, oil	Pyroxasulfone M-1 M-3 M-25	LC/MS/MS	0.01 for M-3 in corn meal and M-1 in corn oil 0.005 for all other analytes in corn matrices
Soybean forage, seed, hay, meal, hulls, oil	Pyroxasulfone M-1 M-3 M-25	LC/MS/MS	0.01 for M-1 in soybean seed and oil 0.005 for all other analytes in soybean matrices
Crop commodity data generation method (Australia)			
Wheat forage, grain, straw	Pyroxasulfone M-1 M-3 M-25	LC/MS/MS (Method No. ATM-0031-02)	0.01
Livestock commodity enforcement method + independent laboratory validation			
Milk, muscle, liver, kidney, fat	Pyroxasulfone M-1 M-3	LC/MS/MS	0.001 for pyroxasulfone, M-1, M-3 in milk; 0.010 for pyroxasulfone, M-1, M-3 in muscle, liver, kidney, and fat
Poultry egg	Pyroxasulfone M-1 M-3	LC/MS/MS	0.01

Crop commodities

Monograph for Pyroxasulfone, Sections B.5.2.1 and B.5.2.3 (MRIDs 47701656-47701658, 47701661, 47701662, 47701665)

Enforcement methods: K-I Chemical has proposed LC/MS/MS enforcement methods for the determination of residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 in/on crop commodities. The methods were developed in conjunction with the corn and soybean field trial studies.

Corn commodities: The method for corn commodities is entitled: *KIH-485/M-3, M-l and M-25 Analytical Method in Corn as Described in "Magnitude of the Residue of KIH-485 WG 85 Herbicide in Corn (field corn and sweet corn) Raw Agricultural Commodities."* The method includes individual instructions for the extraction and analysis of samples of corn grain, forage, stover, grits, flour, starch, meal, and oil.

In general, samples are extracted with ACN:water (3:1, v:v) [grain, oil] or methanol:water (3:1, v:v) [forage, stover, grits, flour] via shaking and sonication (after allowing to soak overnight for grain and stover). The extract is partitioned with hexane, and the hexane phase is discarded. The aqueous layer is diluted to volume with extraction solvent and divided into two aliquots, one for the determination of pyroxasulfone and M-3 and the other for the determination of M-1 and M-25. The pyroxasulfone/M-3 aliquot is concentrated to remove the ACN or methanol, mixed with 0.5 M $NaHCO_3$ and, for grain and oil, saturated NaCl solution, and partitioned twice with hexane. The combined hexane layers, containing pyroxasulfone, are concentrated to near dryness

and reconstituted in ACN. The aqueous phase, containing M-3, is acidified (using 0.5 M citric acid) and partitioned twice with hexane:EtOAc (3:7, v:v); the organic phases are combined, evaporated to dryness, and redissolved in ACN. The pyroxasulfone and M-3 extracts are cleaned up on Envi-Carb solid-phase extraction (SPE) cartridges; the eluates are combined, evaporated to dryness, and redissolved in ACN:water (1:1 or 2:1, v:v) for analysis.

For determination of M-1 and M-25, the ACN/water aliquot is concentrated, mixed with pH 5 acetate buffer [grain, oil] or water [forage, stover, grits, flour], and partitioned with EtOAc. The aqueous phase is either: (1) mixed with saturated NaCl solution and partitioned twice with ACN; the ACN phases are combined, evaporated to dryness, and redissolved in ACN:water (1:9, v:v) for analysis [M-1 in grain and M-1 and M-25 in oil]; (2) diluted with water for analysis [M-25 in grain, stover, grits, flour]; or (3) cleaned up on an NH_2 SPE cartridge and diluted to volume with water for analysis [M-1 in forage, stover, grits, flour, and M-25 in forage].

For corn starch, samples were extracted with ACN:water (3:1, v:v), via shaking and sonication, and the extract was evaporated to dryness and reconstituted in ACN. The extract was cleaned up on an Envi-Carb SPE cartridge; the eluate was evaporated to dryness and redissolved in ACN:water (2:8, v:v) for analysis (pyroxasulfone and M-3 in one aliquot, M-1 in a second aliquot, and M-25 in a third aliquot). For corn meal, samples were extracted with ACN:water (3:1, v:v), via shaking and sonication, and the extract was concentrated, mixed with NaCl and water, and partitioned with ACN. The ACN layer was evaporated to dryness, reconstituted in ACN, and cleaned up on an Envi-Carb SPE cartridge. The eluate was diluted with ACN and divided into two aliquots; one aliquot was used for the determination pyroxasulfone and the other for the determination of M-1, M-3, and M-25. The pyroxasulfone aliquot was evaporated to dryness and redissolved in ACN for analysis. The M-1/M-3/M-25 aliquot was evaporated to dryness and redissolved in ACN:water (1:1, v:v) containing 0.5% acetic acid. The extract was cleaned up on a C-18 SPE cartridge and the eluate was evaporated to dryness and redissolved in ACN:water (2:8, v:v) for analysis (separate aliquot for each of the three analytes).

The petitioner reported that several LC/MS/MS analysis methods were necessary to achieve acceptable recovery; many matrices required more than one method due to varying enhancement from matrix co-extractives. All methods used a C-18 column; methods varied in the solvent system and gradient used. For pyroxasulfone and M-3 in grain, M-3 in stover, grits, and meal, and M-1 and M-25 in all commodities, a gradient of water and ACN, each containing 0.05% formic acid was used. For pyroxasulfone and M-3 in grain, forage, starch, oil, and flour and

pyroxasulfone in stover, grits, and meal, a gradient of water and methanol, each containing 0.05% formic acid, was used. Residues were quantified using a calibration curve of external standards. The method did not include any information about converting residues of metabolites to parent equivalents.

The ion transitions used for quantitation of the pyroxasulfone analyte were the sum of 392 m/z →229 m/z and 392 m/z →179 m/z.

The ion transitions used for quantitation of the M-1 analyte were the sum of 309 m/z →259 m/z and 309 m/z →195 m/z..

The ion transitions used for quantitation of the M-3 analyte were the sum of 259 m/z →215 m/z and 259 m/z →165 m/z.

The ion transitions used for quantitation of the M-25 analyte were were the sum of 295 m/z →181 m/z and 295 m/z →163 m/z..

The LOQ for each analyte in each commodity was 0.005 ppm, except for M-3 in corn meal and M-1 in corn oil, for which the LOQ was found to be 0.01 ppm. The petitioner stated that due to the difficulties encountered in the determination of pyroxasulfone, M-1, M-3 and M-25, some of the analyses were conducted with solvent-based calibrants while others were based on calibrants prepared in control matrix final extract; the matrix-based calibrants were necessary when mass spectral ionization demonstrated significant matrix enhancement or matrix suppression of the signal.

The petitioner stated that matrix blanks (controls) were analyzed concurrently to evaluate potential analytical interferences and that there were no known interferences from corn components or from reagents, solvents and glassware used; results for controls analyzed during method validation were not reported. However, apparent residues of each analyte were below the LOQ in/on all untreated samples from the corn field trials, except that apparent residues of M-3 were found in/on one sample of untreated field corn grain, at 0.006 ppm.

The method was validated in corn forage, grain, stover, grits, starch, meal, flour, and oil by fortification with each analyte at 0.005, 0.01, and 0.10 ppm for pyroxasulfone, M-1, and M-3, and at 0.005 and 0.05 ppm for M-25; corn forage was additionally fortified with pyroxasulfone at 50 ppm. Average recoveries were within acceptable limits (70-120%) for all analytes in all matrices with the following exceptions: pyroxasulfone in corn grits at the 0.005-ppm fortification level (average recovery 65%); M-1 in corn forage and stover at the 0.01- and 0.10-ppm fortification levels (average recoveries 132-156%); and M-25 in corn stover and oil at the 0.05-ppm fortification level (average recoveries of 69% and 57%, respectively). The overall relative standard deviations (RSDs) were <20% for all analytes in all matrices with the following exceptions: pyroxasulfone in corn meal (21%); and M-1 in corn forage and stover (26% each). Recoveries from all matrices ranged 60-120% for pyroxasulfone (average of 88%; four recoveries <70%), 52-157% for M-1 (average of 99%; three recoveries <70% and 12 recoveries >120%), 55-116% for M-3 (average of 88%; four recoveries <70%), and 54-120% for M-25 (average of 86%; five recoveries <70%).

The method was subjected to independent laboratory validation (ILV) using samples of corn grain, forage, stover, grits, starch, meal, flour and oil fortified with pyroxasulfone, M-1, M-3, and M-25 at 0.005 ppm and 0.05 ppm each. The average recoveries were within acceptable limits (70-120%) for all analytes in all matrices with the exception of M-1 in meal (both fortification levels; 142% and 123% average recovery) and M-3 in stover (both fortification levels; 121% and 124% average recovery). The RSDs were <20% for all analytes in all matrices with the exception of M-3 in grits (lower fortification level; 27.2% RSD) and M-25 in stover (lower

fortification level; 28.5% RSD). The ILV laboratory stated that for M-3 in stover, the absence of blank matrix contributions, precision of the replicate values for M-3, and comparable recoveries for both fortification concentrations was considered adequate to validate the method. For M-1 in meal, the ILV laboratory concluded that enhancement of the response was evident at the levels tested.

The ILV laboratory reported that one set of pyroxasulfone, M-1, M-3, and M-25 samples (total of 12 samples) required approximately four days to complete, including LC/MS/MS instrument time for quantitation, and required three full analyst's days for extraction and preparation for analysis. The laboratory recommended that a warning be issued as part of each method that it is not known if the partitions will lead to emulsions, and suggested that for flour, the elution volume for pyroxasulfone for the Envi-Carb SPE extraction cartridge be increased and the volume used for reconstituting the dried eluate be increased; these minor modifications increased the recovery of pyroxasulfone greater than 10%. The registrant has submitted MRID 48430001 which contains the suggestion of the ILV laboratory for a warning regarding emulsions forming along with the corn flour extraction revisions.

Adequate concurrent method recovery data for pyroxasulfone, M-1, M-3, and M-25 in field corn forage, stover, grain, grits, meal, flour, starch, dry or wet milled oil, and sweet corn forage, K+CWHR, and fodder were submitted with the crop field trial and processing study submitted with this petition; samples were fortified at 0.01 and 0.10 ppm for pyroxasulfone, M-1, and M-3 in each matrix, and at 0.005 and 0.05 ppm for M-25 in each matrix. For all analytes, average concurrent recoveries were generally within the acceptable range of 70-120%. Recoveries <70% were observed from corn oil fortified with M-25 at 0.005 and 0.05 ppm (52% and 57%).

Soybean commodities: The method for soybean commodities is entitled: *KIH-485/M-3, M-1 and M-25 Analytical Method in Soybean as Described in "Magnitude of the Residue of KIH-485 WG 85 Herbicide in Soybean Raw Agricultural Commodities."* The method includes individual instructions for the extraction and analysis of samples of soybean seed, forage, hay, hulls, meal, and oil.

In general, samples are extracted with ACN:water (3:1, v:v) [seed, hay, hulls, meal, oil] or methanol:water (3:1, v:v) [forage] via shaking and sonication. The extract is partitioned with hexane, and the hexane phase is discarded. The aqueous layer is diluted to volume with extraction solvent and divided into two aliquots, one for the determination of pyroxasulfone and M-3 and the other for the determination of M-1 and M-25. The pyroxasulfone/M-3 aliquot is concentrated to remove the ACN or methanol, mixed with 0.5 M $NaHCO_3$ and saturated NaCl solution [seed, hay, hulls, meal, oil] or with 0.5 M $NaHCO_3$ only [forage], and partitioned twice with hexane. The combined hexane layers, containing pyroxasulfone, are concentrated to near dryness and reconstituted in ACN. The aqueous phase, containing M-3, is acidified (using 0.5 M citric acid) and partitioned twice with hexane:EtOAc (3:7, v:v); the organic phases are combined, evaporated to dryness, and redissolved in ACN. The pyroxasulfone and M-3 extracts are cleaned up on Envi-Carb SPE cartridges; the eluates are combined, evaporated to dryness, and redissolved in ACN:water (2:1, v:v) for analysis.

For determination of M-1 and M-25, the ACN/water aliquot is concentrated, mixed with pH 5 acetate buffer [M-1 in seed; M-1 and M-25 in hay, hulls, meal, oil] or water [M-25 in seed; M-1

and M-25 in forage], and partitioned with EtOAc. The aqueous phase is either: (1) mixed with saturated NaCl solution and partitioned twice with ACN; the ACN phases are combined, evaporated to dryness, and redissolved in ACN:water (1:9, v:v) for analysis [M-1 in seed, hay, meal; M-1 and M-25 in hulls, oil] or redissolved in water for analysis [M-25 in hay]; or (2) cleaned up on an NH_2 SPE cartridge and diluted to volume with water for analysis [M-25 in seed, meal; M-1 and M-25 in forage].

LC/MS/MS analyses were conducted using a C-18 column and a gradient mobile phase of water and ACN, each containing 0.05% formic acid [for pyroxasulfone and M-3 in seed, hay, and hulls; and M-1 in forage, seed, and hay] or a gradient mobile phase of water and methanol, each containing 0.05% formic acid [for pyroxasulfone and M-3 in forage, seed, hay, meal, and oil; and M-1 and M-25 in all commodities]. Residues were quantified using a calibration curve of external standards. The method did not include any information about converting residues of metabolites to parent equivalents.

The ion transitions used for quantitation of the KIH-485 analyte were the sum of 392 m/z →229 m/z and 392 m/z →179 m/z.

The ion transitions used for quantitation of the M-1 analyte were the sum of 309 m/z →259 m/z and 309 m/z →195 m/z..

The ion transitions used for quantitation of the M-3 analyte were the sum of 259 m/z →215 m/z and 259 m/z →165 m/z.

The ion transitions used for quantitation of the M-25 analyte were were the sum of 295 m/z →181 m/z and 295 m/z →163 m/z..

The LOQ for each analyte in each commodity was 0.005 ppm, except for M-1 in soybean seed and meal, for which the LOQ was found to be 0.01 ppm. The petitioner stated that due to the difficulties encountered in the determination of pyroxasulfone, M-1, M-3, and M-25, some of the analyses were conducted with solvent-based calibrants while others were based on calibrants prepared in control matrix final extract; the matrix-based calibrants were necessary when mass spectral ionization demonstrated significant matrix enhancement or matrix suppression of the signal.

The petitioner stated that matrix blanks (controls) were analyzed concurrently to evaluate potential analytical interferences; results for controls analyzed during method validation were not reported. However, in the soybean field trials, apparent residues of each analyte were below the LOQ in/on untreated samples, with the following exceptions: (1) apparent residues of M-1 were found in/on five samples of untreated soybean forage, at 0.007-0.027 ppm; (2) apparent residues of M-25 were found in/on one sample of untreated forage at 0.011 ppm and one sample of untreated soybean hay, at 0.017 ppm; and (3) apparent residues of pyroxasulfone were found in/on one sample of untreated soybean seed, at 0.020 ppm (residues in/on treated samples from this site were <0.005 ppm). The petitioner believes that the untreated hay sample bearing quantifiable residues of M-25 may have been switched with a treated sample at the same site, as one treated sample bore residues <0.005 ppm and the other bore residues very similar to those found in the untreated sample (0.018 ppm). No other discussion of apparent residues found in untreated samples was provided.

The method was validated in soybean forage, seed, hay, meal, hulls, and oil by fortification with each analyte at 0.005, 0.01, and 0.10 ppm for pyroxasulfone, M-1, and M-3 (0.01 and 0.10 ppm only for M-1 in seed and meal), and at 0.005 and 0.05 ppm for M-25; soybean forage was additionally fortified with pyroxasulfone at 25 ppm, with M-1 at 0.50 ppm, and with M-25 at 0.20 ppm. Average recoveries were within acceptable limits (70-120%) for all analytes in all

matrices with the following exceptions: M-3 in soybean oil at the 0.005-ppm fortification level (average recovery 65%); M-25 in soybean oil at the 0.005-ppm fortification level (average recovery 65%); and M-25 in soybean meal, hulls, and oil at the 0.05-ppm fortification level (average recoveries 62-67%). The RSDs were <20% at for all analytes in all matrices at all fortification levels. Recoveries from all matrices ranged 63-108% for pyroxasulfone (average of 83%; one recovery <70%), 66-120% for M-1 (average of 94%; one recovery <70%), 63-116% for M-3 (average of 84%; four recoveries <70%), and 58-112% for M-25 (average of 81%; seven recoveries <70%).

The method was subjected to ILV using samples of soybean seed, forage, hay, hulls, meal, and oil fortified with pyroxasulfone, M-1, M-3, and M-25 at 0.005 ppm and 0.05 ppm each. The average recoveries were within acceptable limits (70-120%) for all analytes in all matrices with the exception of M-1 in forage (both fortification levels; 66.7 and 69.0% average recovery), M-3 in hay (lower fortification level; 68.0% average recovery), and pyroxasulfone, M-1, and M-25 in hulls (higher fortification level; 67.7-69.9% average recovery). The RSDs were <20% for all analytes in all matrices. For all instances where the mean recovery did not meet the desired, the petitioner concluded that the RSDs were sufficiently small to demonstrate good reproducibility.

The ILV laboratory reported that one set of pyroxasulfone, M-1 and M-3 samples (total of 12 samples) required approximately four days to complete, including LC/MS/MS instrument time for quantitation, and required three full analyst's days for extraction and preparation for analysis. The laboratory recommended that a warning be issued as part of each method that it is not known if the partitions will lead to emulsions, and that for all commodities, the method include the addition of saturated NaCl solution at the step where the aqueous phase is basified with 0.5 M $NaHCO_3$. The registrant has submitted MRID 48430001 which contains the recommendation of the ILV laboratory pertaining to a warning regarding emulsions forming.

Adequate radiovalidation data for this method were submitted using a sample of soybean hay from soybean plants treated postemergence with pyrazole-label [^{14}C]pyroxasulfone (from a soybean metabolism study which does not appear to have been submitted to EPA). The sample bore quantifiable residues of metabolites M-1, M-3, and M-25 but no quantifiable residues of pyroxasulfone. The data indicated that the method adequately recovered incurred residues of M-1, M-3, and M-25 from soybean hay; no quantifiable residues of pyroxasulfone were found in the sample when analyzed using the residue method.

Adequate concurrent method recovery data for pyroxasulfone, M-1, M-3, and M-25 in soybean forage, hay, seed, meal, hulls, and refined oil were submitted with the crop field trial and processing study submitted with this petition; samples were fortified at 0.01 and 0.10 ppm for pyroxasulfone, M-1, and M-3 in each matrix, and at 0.005 and 0.05 ppm for M-25 in each matrix (M-25 was additionally validated at 0.5 ppm in soybean hay). For all analytes, average concurrent recoveries were generally between 70% and 120%. Average recoveries <70% were observed from M-25 in soybean hay and meal at the 0.05-ppm fortification level (67% each) and in soybean oil at both fortification levels (62% and 65%). In addition, soybean seed from the processing study fortified with M-25 at 0.05 ppm yielded a recovery of 64%, soybean hull fortified with M-25 at 0.005 and 0.5 ppm yielded recoveries of 36% and 59%, respectively, and soybean oil fortified with M-1 at 0.10 ppm yielded a recovery of 69%.

Data collection method: An LC/MS/MS method similar to the enforcement methods was used for the determination of residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 in wheat commodities in the wheat field trial studies and in the field pea and wheat commodities in the field rotational crop studies submitted with this petition. The method, ATM-0031, is entitled: *Determination of KIH-485 and the metabolites M-1, M-3 and M-25 in or on plant material by LC MS/MS.* The method includes instructions for the analysis of samples of grain, straw, and forage.

Briefly, water is added to the sample, and the mixture is sonicated and then shaken. ACN is added, to bring the ACN:water ratio to 3:1, and the mixture is sonicated and shaken. The extract is filtered prior to being partitioned with n-hexane. The n-hexane phase is discarded, and an aliquot of the ACN/water phase is analyzed for pyroxasulfone, M-1 and M-3 by LC/MS/MS. For the determination of the M-25 analyte, an aliquot of the ACN/water layer is reduced to dryness and reconstituted in water for LC/MS/MS analysis. Residue levels are quantitated using a calibration curve of matrix-matched standard solutions containing pyroxasulfone, M-1, M-3 and M-25. A single ion transition is monitored for each analyte. The method includes molecular weight conversion factors to allow conversion of metabolite residues to parent equivalents, but does not specify that metabolite results be reported in parent equivalents.

The LOQ, expressed as analyte equivalents, is 0.01 ppm for each analyte in all crop matrices. Apparent residues in the control samples tested were ≤30% of the LOQ.

The method was validated in cereal forage, grain, and straw; the petitioner did not identify the crop used for method validation studies. Samples were fortified with each analyte at the LOQ and 10xLOQ. Average recoveries were within acceptable limits (70-120%) and RSDs were <20% at both the 0.01- and 0.1-ppm fortification levels for pyroxasulfone and the M-1, M-3 and M-25 metabolites. Recoveries from all three matrices ranged 73-112% for pyroxasulfone (average of 91%), 70-109% for M-1 (average of 92%), 76-110% for M-3 (average of 91%), and 70-104% for M-25 (average of 85%).

Adequate concurrent method recovery data for pyroxasulfone, M-1, M-3, and M-25 in wheat forage, grain, and straw were submitted with the crop field trial studies submitted with this petition; samples were fortified with each analyte at 0.01 and 0.10 ppm. For all analytes, average concurrent recoveries were between 70% and 120%.

Conclusions. The submitted residue analytical method data are adequate to satisfy data requirements. The methods are adequate to determine pyroxasulfone residues of concern in corn, soybean, and wheat commodities. For the corn and soybean commodity methods to be considered adequate for enforcement purposes, the methods were required to be modified to include the recommendations of the independent laboratory and to include instructions for reporting metabolite residues in parent equivalents. Finally, the methods were required to be amended to include instructions for the analysis of wheat commodities. The petioner submitted these data which were acceptable (T. Morton, D389651, 5/25/11).

HED consulted Charles Stafford (personal communication via email July 20, 2010) who stated the crop enforcement method would not need to be forwarded to ACB for validation.

Livestock commodities

Monograph for Pyroxasulfone, Section B.5.2.2 (MRIDs 47701659, 47701660, 47701663, 47701664)

Data collection methods: An LC/MS/MS method was used for the determination of residues of pyroxasulfone and its metabolites M-1 and M-3 in cattle commodities in the cattle feeding study submitted with this petition. In addition, the petitioner submitted an LC/MS/MS method for the determination of residues of pyroxasulfone, M-1, and M-3 in poultry eggs.

Cattle commodities: The method for cattle commodities is entitled: *KIH-485, M-3 and M-l Analytical Methods as Described in "Magnitude of KIH-485 Residues in Bovine Tissues and Milk from a 28-Day Feeding Study."* The method includes individual instructions for the extraction and analysis of samples of milk, muscle, liver, kidney, and fat.

For determination of pyroxasulfone and M-3, samples of milk, cream, and skim milk are extracted twice with ACN:water (3:1, v:v), and the combined extracts are partitioned with hexane, with the hexane phase discarded. The aqueous ACN extracts are diluted to volume with ACN:water (3:1, v:v), and an aliquot is concentrated, basified (using 0.5 M NaHCO3), mixed with saturated NaCl solution, and partitioned with hexane to extract pyroxasulfone. The hexane phase is concentrated to dryness and reconstituted in ACN for further Envi-Carb SPE cleanup and subsequent LC/MS/MS analysis for pyroxasulfone. The aqueous portion is acidified (to ~pH 4 using 0.5 M citric acid) then partitioned with hexane:EtOAc (3:7, v:v) to extract M-3. The organic phase is cleaned up on an Envi-Carb SPE cartridge for LC/MS/MS analysis.

Milk samples are analyzed separately for residues of M-1. The proteins are precipitated with acetone and the supernatant is concentrated to remove the acetone. The aqueous extract is partitioned twice with hexane and the aqueous phase is mixed with saturated NaCl solution and partitioned with ACN. The ACN phase is concentrated to dryness and redissolved in ACN:water (1:9, v:v) for LC/MS/MS analysis.

Samples of tissues are homogenized with water and extracted twice with ACN. The combined extracts are partitioned with hexane, and the hexane phase is back partitioned with ACN, after which the hexane phase is discarded. The ACN:water extracts are combined, brought to volume (using an unspecified solvent), and divided into two aliquots, one for determination of pyroxasulfone and M-3, and the other for determination of M-1. The pyroxasulfone and M-3 aliquot is basified (using 0.5 M $NaHCO_3$), mixed with saturated NaCl solution, and partitioned with hexane to extract pyroxasulfone. The hexane phase is concentrated to dryness and reconstituted in ACN for further Envi-Carb SPE cleanup; the extract is evaporated to dryness and reconstituted in ACN:water (2:8, v:v, containing 0.5% acetic acid) for LC/MS/MS analysis for pyroxasulfone. The aqueous portion is acidified (using 0.5 M citric acid) then partitioned with hexane:EtOAc (3:7, v:v) to extract M-3. The extract is evaporated to dryness and reconstituted in ACN:water (2:8, v:v, containing 0.5% acetic acid) for LC/MS/MS analysis for M-3. The aliquot for M-l determination was concentrated, diluted to volume with water (muscle, kidney, liver) or acidified to pH 5 (using 0.2 M acetic buffer; fat), and partitioned twice with EtOAc. The aqueous phase is mixed with NaCl, and residues of M-l are partitioned into ACN. The ACN extract is evaporated to dryness and reconstituted in ACN:water (2:8, v:v, containing 0.5% acetic acid) for analysis by LC/MS/MS.

LC/MS/MS analyses were conducted using a C-18 column with a gradient mobile phase of ACN and water, each containing 0.05% formic acid (for determination of pyroxasulfone and M-3), or water and methanol, each containing 0.05% formic acid (for determination of M-1). Residues were quantified using a calibration curve of external standards. The method did not include any information about converting residues of metabolites to parent equivalents.

The LOQ was 0.01 ppm for each analyte in tissues and 0.001 ppm for each analyte in milk. The petitioner stated that matrix blanks (controls) were analyzed concurrently to evaluate potential analytical interferences, and in all cases where there was enhanced residue recovery (>120%), there were no residues detected for pyroxasulfone, M-1 or M-3. Results for controls analyzed during method validation were not reported. In the cattle feeding study, apparent residues of each analyte were below the LOQ in/on all samples of milk, skim milk, cream, muscle, fat, liver, and kidney from the undosed cattle.

The method was validated in milk by fortification with pyroxasulfone, M-1, and M-3 at 0.001 and 0.010 ppm each and was validated in muscle, liver, kidney and fat by fortification with each analyte at 0.01 and 0.10 ppm each. Average recoveries were within acceptable limits (70-120%) for all analytes in all matrices. The RSDs were <20% for all analytes in all matrices at all fortification levels, with the following exceptions: pyroxasulfone in muscle at the 0.01-ppm fortification level (23%) and M-1 in liver at the 0.10-ppm fortification level (21%). Recoveries from all matrices ranged 83-130% for pyroxasulfone (average of 94%; one recovery >120%), 66-136% for M-1 (average of 95%; one recovery <70% and two recoveries >120%); and 86-118% for M-3 (average of 102%).

The method was subjected to ILV using samples of cattle milk, muscle, liver, kidney, and fat fortified with pyroxasulfone, M-1, and M-3, at 0.001 ppm and 0.01 ppm each for milk and 0.01 and 0.10 ppm each for tissues. The average recoveries were within acceptable limits (70-120%) for all analytes in all matrices with the exception of M-1 in liver (0.10-ppm fortification level; 122% average recovery), M-3 in liver (0.01-ppm fortification level; 68.1% average recovery), and M-3 in kidney (0.01-ppm fortification level; 121% average recovery). The RSDs were <20% for all analytes in all matrices. The average recoveries outside the 70-120% range were accepted by the petitioner as adequate validation based on the high precision of the replicate analyses (≤4.7% RSD). The ILV laboratory stated that one set of samples (total of 12 samples) required approximately four days for completion, including LC/MS/MS instrument time for quantitation, and required three full analyst's days for extraction and preparation for analysis.

No radiovalidation data were submitted for the method.

Poultry eggs: An LC/MS/MS method was submitted for the determination of residues of pyroxasulfone and its metabolites M-1 and M-3 in poultry eggs.

Samples of egg are homogenized with water and extracted twice with ACN. The combined extracts are partitioned with hexane, and the hexane phase is back partitioned with ACN, after which the hexane phase is discarded. The ACN/water extracts are combined, brought to volume using ACN:water (9:1, v:v), and divided into two aliquots, one for the determination of pyroxasulfone and M-3 and the other for the determination of M-1. The pyroxasulfone and M-3 aliquot is concentrated, basified (using 0.5 M $NaHCO_3$), mixed with saturated NaCl solution, and

partitioned three times with hexane. The combined hexane extract is concentrated to dryness and reconstituted in ACN for further purification by Envi-Carb SPE; the extract is evaporated to dryness and reconstituted in ACN:water (2:8, v:v, containing 0.5% acetic acid) for LC/MS/MS analysis for pyroxasulfone. The aqueous portion remaining after the hexane partition is acidified (using 0.5 M citric acid), and M-3 is partitioned into hexane:EtOAc (3:7, v:v). The organic phase is evaporated to dryness and reconstituted in ACN:water (2:8, v:v, containing 0.5% acetic acid) for analysis by LC/MS/MS. The M-1 aliquot of the original extract is concentrated, acidified to pH 5 (using 0.2 M acetate buffer), and partitioned with EtOAc. The remaining aqueous phase is purified by NH_2 SPE for LC/MS/MS analysis.

LC/MS/MS analyses were conducted using a C-18 column with a gradient mobile phase of ACN and water, each containing 0.05% formic acid (for determination of pyroxasulfone and M-3), or water and methanol, each containing 0.05% formic acid (for determination of M-1). Residues were quantified using a calibration curve of external standards. The method did not include any information about converting residues of metabolites to parent equivalents.

The LOQ was 0.01 ppm for each analyte in poultry egg. The petitioner stated that matrix blanks (controls) were analyzed concurrently to evaluate potential analytical interferences; no analytical interferences were detected in matrix blanks (the limit of detection was 0.0005 ppm for pyroxasulfone and M-3 and 0.0025 ppm for M-1).

The method was validated in poultry egg by fortification with pyroxasulfone, M-1, and M-3 at 0.01 and 0.10 ppm each. Average recoveries were within acceptable limits (70-120%) and the RSDs were <20% for all analytes. Recoveries ranged 81-124% for pyroxasulfone (average of 100%; one recovery >120%), 65-95% for M-1 (average of 83%; one recovery <70%); and 91-111% for M-3 (average of 102%).

The method was subjected to ILV using samples of poultry egg fortified with pyroxasulfone, M-1, and M-3 at 0.01 and 0.10 ppm each. The average recoveries were within acceptable limits (70-120%) for all analytes with the exception of M-3 at the 0.01-ppm fortification level (131% average recovery). The RSDs were <20% for all analytes at both fortification levels. The high average recovery for M-3 at the LOQ was accepted by the petitioner as adequate validation based on the high precision of the replicate analyses (3.1% RSD) and the absence of any integrated response for M-3 matrix blanks. The ILV laboratory stated that one set of samples (total of 12 samples) required approximately four days to complete, including LC/MS/MS instrument time for quantitation, and required three full analyst's days for extraction and preparation for analysis.

No radiovalidation data were submitted for the method.

Conclusions. The submitted residue analytical methods data are partially adequate to satisfy data requirements. Radiovalidation data must be submitted for the method for cattle commodities.

HED notes that for the method for poultry egg to be considered adequate for data collection purposes, radiovalidation data would be required. However, these data are not required at this time because no poultry feeding study data are required to support this petition.

The petitioner is not proposing tolerances for livestock commodities in the U.S. HED notes that for the above method(s) to be considered adequate for enforcement purposes, the method(s) would need to be modified to include the recommendations of the independent laboratory and to include instructions for reporting metabolite residues in parent equivalents. In addition, radio-validation data are required.

860.1360 Multiresidue Methods

Monograph for Pyroxasulfone, Section B.5.2.4 (MRID 47701673)

K-I Chemical submitted data on the testing of pyroxasulfone, and its three principle metabolites, M-1, M-3, and M-25, through a select portion of the FDA PAM multiresidue methods.

None of the test substances are N-methyl carbamates and none were found to be naturally fluorescent; therefore, the compounds were not further tested under Protocol A.

Supplementary testing through the FDA-Pesticide Analytical Methods Multi-Residue testing program (Chapters 3 and 4) in accordance with OPPTS test guideline 860.1360 was conducted in response to the U.S. EPA review of the above study (MRID 47701673). The new study presents data concerning Protocol B testing of metabolites M-1, M-3, and M-25 via methyl derivatives and the recovery of KIH-485 from a high moisture matrix, sweet corn kernel + cob with husks removed (K+CWHR) through Protocol D testing. None of the three acidic metabolite compounds, M-1, M-3, or M-25, was successfully recovered through Protocol B.

KIH-485 was partially to completely recovered from sweet corn K+CWHR using Protocol D, extraction method E-2, and cleanup method C5 with average recoveries of 71.68% and 92.39% at fortification levels of 0.026 and 0.208 ppm. A slight analytical interference was observed.

With the submission of these supplementary data, the requirements for multiresidue methods testing of pyroxasulfone and its metabolites have been satisfied (T. Morton D396692, 12/8/11). The data indicate that the PAM Vol. I multiresidue methods, including Protocol D (report IIA 4.3/14) and Protocols E and F (report IIA 4.3/11) may be applicable for determination of pyroxasulfone *per se*; however, the FDA multiresidue methods are not suitable for determination of the metabolites M-1, M-3, and M-25.

None of the metabolite compounds could be successfully chromatographed under Protocol C; pyroxasulfone chromatographed by GLC/ECD with adequate selectivity, sensitivity, and linearity.

Pyroxasulfone was found to be fully recovered from soybean hay through PAM Section 303 (Protocol E) with extraction procedure E4 and cleanup method C1; average recovery was 91.85% in samples fortified at 0.545 and 0.0545 ppm. In addition, pyroxasulfone was recovered from soybean seed and oil through PAM Section 304 (Protocol F) with extraction procedure E5 and either cleanup method C1 or C2; average recovery was 90.05% for seed fortified at 0.218 and 0.0218 ppm and 67.1% for oil fortified at 0.363 and 0.0363 ppm. The petitioner did not test Protocol D (PAM Section 302) because the sample matrix used for testing (soybean hay) did not have a high moisture content.

Because pyroxasulfone and its metabolites are not substituted ureas, no testing under Protocol G is required.

Conclusions. The submitted studies are adequate to satisfy data requirements. In addition, if metabolite M-28 is determined to be a residue of concern in soybeans, it will need to be tested also.

The data have been sent to FDA for evaluation.

860.1380 Storage Stability

Crop commodities

Monograph for Pyroxasulfone, Section B.7.6.2 (MRIDs 47701656, 47701657, 48430011)

K-I Chemical submitted interim reports for two ongoing storage stability studies: one study with corn commodities and one study with soybean commodities.

In the corn study, samples of corn forage, grain, stover, starch, flour, meal, and oil were fortified with pyroxasulfone, M-1, M-3, and M-25 at 0.10 or 0.05 ppm each. The fortified samples were stored in glass jars at <0 °C for periods including 3-4 months, 6-7 months, and the longest period necessary to encompass total storage time of field samples. The study was conducted concurrently with the corn field trial study.

At each storage interval, residues of pyroxasulfone and its metabolites were determined using the proposed LC/MS/MS enforcement method for corn commodities. The mean of the concurrent recoveries for all matrices at all tested intervals was within the acceptable range of 70-120%, with the exception of M-1 in oil at the 4-month interval (average of 65%) and M-3 in starch at the 4-month interval (average of 69%) and M-25 in oil (4-, 6-, 13-, and 17-month intervals; average of 50%, 69%, 69% and 68%, respectively) and starch (7-month interval; average of 64%).

Pyroxasulfone (KIH-485) and metabolites M-1 and M-3 were found to be stable in corn stover through 12 months of frozen storage and in corn grain and forage through 13 months of frozen storage. Pyroxasulfone, M-1, and M-3 were found to be stable in corn processed commodities during 6 months (oil) or 7 months (starch, flour, and meal) of frozen storage. M-25 residues were stable in forage for 24 months, grain for 26 months, stover for 25 months, starch for 16 months, flour for 23 months, and meal for 18 months. M-25 residues in com oil were moderately stabile at 67% remaining after 17 months of frozen storage.

The aged recovery samples showed excess recovery of M-1 (i.e., >100%) in each RAC matrix at some storage intervals. The petitioner stated that this may be due to LC/MS/MS enhancement from aged matrix. When corrected for fresh fortification recovery, M-1 recovery in stover at the 12-month storage interval was low (62%); the uncorrected recovery was adequate.

In the soybean study, samples of soybean forage, seed, hay, meal, hulls, and refined oil were fortified with pyroxasulfone, M-1, M-3, and M-25 at 0.05, 0.10, or 0.20 ppm each. The fortified samples were stored in glass jars at <0 °C for periods including 3-6 months, 6-7 months, and the

longest period necessary to encompass total storage time of field samples. The study was conducted concurrently with the soybean field trial study.

At each storage interval, residues of pyroxasulfone and its metabolites were determined using the proposed LC/MS/MS enforcement method for soybean commodities. The mean of the concurrent recoveries for all matrices at all tested intervals was within the acceptable range of 70-120%, with the exception of M-3 in hay at the 4- and 6-month intervals (average of 161% and 65%, respectively) and M-25 in hay, meal, and hulls at the 5/6-month storage interval (average of 59-63%).
Pyroxasulfone was found to be stable in soybean forage and hay through as much as 17 months of storage, where no significant degradation of the residue was observed. Pyroxasulfone was found to be stable during up to 19 months frozen storage in seed, up to 7 months in refined oil, and up to 10 months storage in meal and hulls. M-1 was found to be stable in forage and hay for up to 17 months, up to 6 months in seed, up to 7 months in oil, and up to 10 months in meal and hulls. M-1 declined by approximately 40% in soybean seed at 19 months of frozen storage. M-3 was found to be stable in forage and hay up to a 17-month period of storage up to a 19-month storage interval in seed, and up to 10 months in oil, meal, and hulls. Some decline in M-1 and M-3 was detected within 7 months and 10 of frozen storage, respectively, in refined oil, while both analytes were found to be stable in meal and hulls for up to 10 months of frozen storage. M-25 was found to be stable in forage hay, and seed after 12 months of frozen storage, in oil after 13 months of frozen storage, and in hulls and meal after 14 months of frozen storage.

The petitioner stated that the remaining time points for M-25 necessary to bracket sample storage prior to extraction will be added to the report by report amendment.

The storage durations and conditions of samples from the crop field trial, processing studies, and field rotational crop studies submitted to support this petition are presented in Table 5.

Table 5. Summary of Storage Conditions and Durations of Samples from Crop Field Trial, Processing, and Field Rotational Crop Studies.

Matrix	Storage Temperature (°C)	Maximum Storage Duration	Interval of Demonstrated Storage Stability
Pyroxasulfone, M-1, and M-3 determination			
Corn forage	Frozen	332 days (10.9 months)	13 months
Corn grain and K+CWHR	Frozen	391 days (12.8 months)	13 months (grain)
Corn grain for processing	Frozen	337 days (11.1 months)	13 months (grain)
Corn stover	Frozen	357 days (11.7 months)	12 months
Corn processed commodities	Frozen	196 days (6.4 months)	6 months (oil) 7 months (starch, flour, and meal)
Soybean forage	Frozen	466 days (15.3 months)	17 months
Soybean hay	Frozen	452 days (14.9 months)	17 months
Soybean seed	Frozen	359 days (11.8 months)	19 months
Soybean seed for processing	Frozen	364 days (12.0 months)	19 months
Soybean meal and hulls	Frozen	231 days (7.6 months)	10 months
Soybean oil	Frozen	220 days (7.2 months)	7 months

Table 5. Summary of Storage Conditions and Durations of Samples from Crop Field Trial, Processing, and Field Rotational Crop Studies.			
Matrix	Storage Temperature (°C)	Maximum Storage Duration	Interval of Demonstrated Storage Stability
Wheat forage	Frozen	58 weeks (13.3 months)	13 months (corn forage)
Wheat grain and straw	Frozen	36 weeks (8.3 months)	13 months (corn grain) 12 months (corn stover)
Rotated field pea forage	Frozen	34 weeks (7.8 months)	17 months (soybean forage)
Rotated field pea seed and straw	Frozen	14 weeks (3.2 months)	17 months (soybean hay) 19 months (soybean seed)
Rotated wheat forage	Frozen	34 weeks (7.8 months)	13 months (corn forage)
Rotated wheat grain and straw	Frozen	14 weeks (3.2 months)	13 months (corn grain) 12 months (corn stover)
M-25 determination			
Corn forage	Frozen	710 days (23.3 months)	24 months
Corn grain and K+CWHR	Frozen	777 days (25.5 months)	26 months (grain)
Corn grain for processing	Frozen	689 days (22.6 months)	26 months (grain)
Corn stover	Frozen	747 days (24.5 months)	25 months
Corn starch	Frozen	479 days (15.7 months)	16 months
Corn grits, flour, and meal	Frozen	520 days (17.1 months)	18 months (meal) 23 months (flour)
Corn oil	Frozen	575 days (18.9 months)	17 months (33% degradation)
Soybean forage	Frozen	799 days (26.3 months)	12 months
Soybean hay	Frozen	727 days (23.9 months)	12 months
Soybean seed	Frozen	891 days (29.3 months)	12 months
Soybean seed for processing	Frozen	720 days (23.7 months)	12 months
Soybean hulls	Frozen	519 days (17.1 months)	14 months
Soybean meal	Frozen	567 days (18.6 months)	14 months
Soybean oil	Frozen	497 days (16.3 months)	13 months
Wheat forage	Frozen	58 weeks (13.3 months)	12 months (corn forage)
Wheat grain and straw	Frozen	36 weeks (8.3 months)	12 months (corn grain and stover)
Rotated field pea forage	Frozen	34 weeks (7.8 months)	12 months (soybean forage)
Rotated field pea seed and straw	Frozen	14 weeks (3.2 months)	12 months (soybean hay) 12 months (soybean seed)
Rotated wheat forage	Frozen	34 weeks (7.8 months)	12 months (corn forage)
Rotated wheat grain and straw	Frozen	14 weeks (3.2 months)	12 months (corn grain and stover)

Conclusions. The submitted data are not adequate to completely satisfy data requirements because the available data represent storage intervals shorter than those of samples from the residue trials. The final reports of the ongoing storage stability studies must be submitted. The final reports should include data for M-25 in soybean raw agricultural commodities and soybean processed commodities.

With submission of the final reports, the petitioner should include additional information/data pertaining to the procedures used for the storage stability studies, including identification of the

fortification levels for each analyte in each matrix, a correct listing of the fortification dates (and storage intervals) for each of the spiked samples, and a discussion of any problems encountered during completion of the studies. An explanation should be provided for not using the data from the 3-month storage interval for M-1 in soybean forage. All residue data spreadsheets for storage stability analyses should be provided.

HED notes that no zero-day data were provided with the study. The petitioner should note for future submissions that storage stability studies should always include a zero-day sampling interval to establish the residue levels present at the time samples are placed into storage [see OPPTS 860.1380(d)(6)(i)].

Livestock commodities

Monograph for Pyroxasulfone, Section B.7.8.3 (MRID 47701659)

K-I Chemical submitted a storage stability study with cattle matrices in conjunction with the cattle feeding study.

Samples of cattle milk, muscle, liver, kidney, and fat were fortified with pyroxasulfone, M-1, and M-3 at 0.01 ppm each for milk and 0.10 ppm each for tissues. The fortified samples were stored frozen (temperature unspecified) for periods of 189 days for milk, 112 days for muscle, up to 120 days for liver, 113 days for kidney, and 91 days for fat. The study was conducted concurrently with the cattle feeding study.

At each storage interval, residues of pyroxasulfone and its metabolites were determined using the LC/MS/MS data collection method for cattle commodities. The mean of the concurrent recoveries for all matrices at the tested intervals was within the acceptable range of 70-120%.

The data indicate that residues of pyroxasulfone, M-l, and M-3 are stable through 6 months of frozen storage in milk, 3 months of frozen storage in fat, and 3.7 months of frozen storage in muscle and kidney. Residues of M-1 and M-3 were stable in liver during up to 4 months of frozen storage. Pyroxasulfone was found to degrade in liver, yielding 40% recovery after 120 days of frozen storage. Short-term storage stability was adequate for pyroxasulfone in liver, where 94% was recovered after 15 days of frozen storage.

In the cattle feeding study, the maximum frozen storage intervals were 154 days for milk samples, 186 days for cream samples, and 87 days for muscle, liver, kidney and fat samples.

Conclusions. The submitted data are adequate to satisfy data requirements. The data indicate that pyroxasulfone residues in liver may need to be adjusted to account for potential decline during storage.

HED notes that as for the crop commodity storage stability studies, no zero-day data were provided with the study.

860.1400 Water, Fish, and Irrigated Crops

There are no proposed uses that are relevant to this guideline topic.

860.1460 Food Handling

There are no proposed uses that are relevant to this guideline topic.

860.1480 Meat, Milk, Poultry, and Eggs

Monograph for Pyroxasulfone, Sections B.7.8.1 and B.7.8.2 (MRID 47701659)

There are several livestock feedstuffs associated with the proposed uses of pyroxasulfone: aspirated grain fractions; field and sweet corn forage, silage, and stover; field corn grain and milled byproducts; sweet corn cannery waste. The dietary burdens of pyroxasulfone to livestock were calculated using the procedures of the most recent guidance developed by HED (June 2008); see Table 6. The estimated dietary burdens are 0.048 ppm for beef cattle, 0.074 ppm for dairy cattle, 0.019 ppm for poultry, and 0.021 ppm for swine. K-I Chemical submitted a feeding study with cattle, which is summarized below, and requested a waiver of the requirement for a poultry feeding study.

Table 6. Calculation of Dietary Burdens of Pyroxasulfone Residues to Livestock.

Feedstuff	Type[1]	% Dry Matter[2]	% Diet[2]	Highest Residue (ppm)	Dietary Contribution (ppm)[3]
Beef Cattle					
Corn, field, stover	R	83	15	0.139	0.025
Corn, field, grain	CC	88	80	0.025	0.023
Untreated Protein Concentrate	PC	NA	5	0	0
TOTAL BURDEN	--	--	100	--	**0.048**
Dairy Cattle					
Corn, field, forage/silage	R	40	45	0.054	0.061
Corn, field, grain	CC	88	45	0.025	0.013
Untreated Protein Concentrate	PC	NA	10	0	0
TOTAL BURDEN	--	--	100	--	**0.074**
Poultry					
Corn, field, grain	CC	88	75	0.025	0.019
Untreated Protein Concentrate	PC	NA	25	0	0
TOTAL BURDEN	--	--	100	--	**0.019**
Swine					
Corn, field, grain	CC	88	85	0.025	0.021
Untreated Protein Concentrate	PC	NA	15	0	0
TOTAL BURDEN	--	--	100	--	**0.021**

[1] R: Roughage; CC: Carbohydrate concentrate; PC: Protein concentrate.
[2] OPPTS 860.1000 Table 1 Feedstuffs (June 2008).
[3] Contribution = ([tolerance /% DM] X % diet) for beef and dairy cattle; contribution = ([tolerance] X % diet) for poultry and swine.

Cattle: The magnitude of the residue of pyroxasulfone and metabolites M-1 and M-3 in dairy cow tissues and milk was determined in a feeding study. For 28 consecutive days, lactating dairy cows were administered pyroxasulfone at a target dose level of 1.8 ppm (estimated by the

petitioner to be 1x, designated "group 2") and at exaggerated target dose levels of 5.4 ppm (designated "group 3") and 18 ppm (designated "group 4"). A control group (designated "group 1") was not dosed. A total of 14 cows were included in the study, two in group 1, three each in groups 2 and 3, and six in group 4. The average daily dose of pyroxasulfone was 36.3 mg/cow/day for group 2, 109.3 mg/cow/day for group 3 and 364.2 mg/cow/day for group 4. The dose levels of 1.8, 5.4, and 18 ppm represent ~38x, 110x, and 370x, respectively, the maximum estimated dietary burden to beef cattle and 24x, 73, and 240x, respectively, the maximum estimated dietary burden to dairy cattle.

Animals were observed twice daily for any clinical signs of toxicity or ill health. Body weights were determined at weekly intervals, and feed consumption was monitored daily. Milk yields were recorded twice daily.

Milk samples from each animal were collected twice daily and combined as one pooled sample. On days 13 and 28, milk samples from all cows, except those cows designated for the depuration phase and cows from the mid dose group, were separated into cream and skim milk for separate analysis. Animals were sacrificed within 24 hours after the final dosing, and tissue samples were taken, except for three cows of the high dose group which were sacrificed 4, 8, and 15 days after the final dose to determine residue levels post dosing. All samples were stored frozen prior to analysis. Samples were analyzed for residues of pyroxasulfone, M-1, and M-3 using the LC/MS/MS data collection method for cattle commodities (described under 860.1340). The LOQ was 0.001 ppm for each analyte in milk matrices and 0.01 ppm for each analyte in tissues.

The longest storage interval from sampling until analysis for any matrix was 186 days for cream samples, 87 days for tissue samples and 154 days for milk samples. Storage stability analyses showed that all analytes were stable in milk for up to 6 months frozen storage and tissues for up to at least 3 months of frozen storage, except for pyroxasulfone in liver which showed only a 40% recovery after 120 days of storage; recovery was 94% after 15 days of storage.

Samples of milk from day 7 were the only milk samples analyzed for the low- and mid-dose groups. For the control and high-dose groups, milk samples from study days 1, 2, 3, 4, 5, 6, 7, 10, 13, 16, 19, 22, 25, and 28 were analyzed. There were no residues of pyroxasulfone or its metabolites M-1 or M-3 in milk greater than the LOQ (0.001 ppm) at any dose level (including the control) except for three milk samples from cows at the high dosing level where pyroxasulfone was found at 0.002-0.004 ppm on study day 7. Skim milk and cream samples from study days 13 and 28 for the control, low-, and high-dose groups were analyzed. No residues of pyroxasulfone or its metabolites M-1 or M-3 were found above LOQ (0.001 ppm) in any samples.

No residues of pyroxasulfone or its metabolites M-1 or M-3 were found greater than the LOQ (0.01 ppm) in any tissue samples (liver, kidney, subcutaneous fat, abdominal fat, perinephric fat, loin muscle, and round muscle) from cattle in the control and high dose groups. No tissue samples from the low and mid dose group were analyzed.

No residues of pyroxasulfone or its metabolites M-1 or M-3 were found greater than the LOQ in any of the samples taken from cows sacrificed during the depuration period (including samples

from the control group). Milk samples were collected 3, 7, and 14 days following the end of dosing.

The results for maximum residues of pyroxasulfone and its metabolites detected at the high-dose level (18 ppm) are summarized in Table 7 below.

Table 7. Maximum Residues in Samples from Cows Dosed at 18 ppm.

Samples	Residues (ppm)		
	Pyroxasulfone	M-1	M-3
Whole milk	<0.004[1]	<0.001	<0.001
Skim milk	<0.001	<0.001	<0.001
Cream	<0.001	<0.001	<0.001
Round Muscle	<0.01	<0.01	<0.01
Loin muscle	<0.01	<0.01	<0.01
Liver	<0.01	<0.01	<0.01
Kidney	<0.01	<0.01	<0.01
Subcutaneous fat	<0.01	<0.01	<0.01
Abdominal fat	<0.01	<0.01	<0.01
Perinephric fat	<0.01	<0.01	<0.01

[1] Day 7 samples only; residues in samples from all other sampling days were <0.001 ppm.

If the nonquantifiable residues of pyroxasulfone in liver from the high-dose cattle are adjusted for potential decline during storage of 45% (estimated decline after 3 months of storage), residues would be <0.02 ppm.

Conclusions. The submitted cattle feeding study is adequate to satisfy data requirements. HED note that radiovalidation data for the analytical method have not yet been submitted (refer to 860.1340) and that the results of the goat metabolism study indicated that radioactivity was not readily extractable from milk and tissues using organic solvents.

The submitted data indicate that tolerances are not needed for cattle tissues and milk at this time for the corn use. Residues of each analyte were <0.01 ppm at a dosing level corresponding to 240x the estimated dietary burden to dairy cattle. Pending submission of radiovalidation data for the analytical method, HED concludes that the proposed uses of pyroxasulfone fall under category 3 of 40 CFR 180.6(a) for ruminant tissues; there is no reasonable expectation of finite residues in cattle, goat, hog, horse, and sheep tissue commodities.

Typically, for a conclusion to be made that no tolerances are needed for livestock commodities, the feeding study data need to indicate that residues are below the LOQ at a 10x dosing level.

For this study, quantifiable residues of parent were found in milk, at up to 0.004 ppm, at a 240x dosing level. If these residues are adjusted to a 10x dosing level (~0.00017 ppm), they are below the LOQ for milk.

Poultry: The petitioner concluded that residues of pyroxasulfone and its major metabolites are not expected to accumulate above the LOQ in poultry matrices destined for human consumption. In the corn, soybean, and wheat field trials, residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ in/on all samples of grain and seed, except one soybean trial in which residues of M-3 in seed were approximately twice the LOQ and two other trials where M-25 residues in seed were just above the LOQ. Of the processed matrices consumed by poultry, soybean meal and hulls had residues of M-3 just above the LOQ. No quantifiable residues were found in corn processed commodities; a wheat processing study has not yet been conducted. Based on these results and the results of the poultry metabolism studies, the petitioner concluded that a poultry feeding study is unnecessary.

In the poultry metabolism studies, the maximum residues observed for an individual identified metabolite were 0.039 ppm of M-1 in liver. Assuming a feeding level of ~780x (based on the 14.8-ppm dosing level and a dietary burden of 0.019 ppm), expected residues of M-1 at a 10x feeding level would be <0.0001 ppm. Therefore, HED concludes that a poultry feeding study is not needed at this time. The proposed uses of pyroxasulfone fall under category 3 of 40 CFR 180.6(a) for poultry; there is no reasonable expectation of finite residues in poultry commodities. The petitioner should note that a poultry feeding study may be needed in the future if additional uses with poultry feedstuffs are proposed. In addition, tolerances on livestock commodities may be needed in the future, if use on additional feed stuffs are requested.

860.1500 Crop Field Trials

Monograph for Pyroxasulfone, Section B.7.6.1.1 (MRID 47701656; field and sweet corn)
Monograph for Pyroxasulfone, Section B.7.6.1.2 (MRID 47701657; soybean)
Monograph for Pyroxasulfone, Section B.7.6.1.3 (MRIDs 47701669, and 47701670; wheat)

K-I Chemical submitted field trial data from corn and soybean field trials conducted in the U.S. and wheat field trials conducted in Australia. The results from these field trials are discussed below and summarized in Table 8. The LOQ for corn grain residues of concern (pyroxasulfone and M-3) is 0.013 ppm.

For all three studies, HED converted residues of metabolites to parent equivalents for calculation of total residues; molecular weight conversion factors of 1.262 for M-1, 1.504 for M-3, and 1.321 for M-25 were used. The full LOQ value was used for residues <LOQ for calculating total residues.

HED notes that K-I Chemical also submitted field trial data for barley and triticale to support use of pyroxasulfone on these crops on Australia. Because pyroxasulfone is not proposed for use on barley or triticale in the U.S., these data will not be discussed herein.

Table 8. Summary of Residue Data from Crop Field Trials with Pyroxasulfone.									
Crop matrix	Target Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Total Residues of Pyroxasulfone and Metabolites M-1, M-3, and M-25 (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.[3]
CORN (proposed use = 0.267 lb ai/A total application rate, 37-day PHI for sweet corn K+CWHR, 7-day PGI for corn forage)									
Field corn forage	0.148-0.268 [166-300][4]	37-95	44	<0.025	<0.054	0.053	0.025	0.028	0.007
Field corn grain		69-146	43	<0.025	<0.025	0.025	0.025	0.025	NA
Field corn stover		85-146	44	<0.025	<0.139	0.131	0.025	0.031	0.022
Sweet corn forage	0.148-0.268 [166-300][4]	43-97	24	<0.025	<0.063	0.063	0.032	0.035	0.011
Sweet corn K+CWHR		43-132	24	<0.025	<0.028	0.028	0.025	0.026	0.001
Sweet corn stover		70-132	24	<0.025	0.115	0.112	0.025	0.0.41	0.028
SOYBEAN (proposed use = 0.267 lb ai/A total application rate, 15-day PHI for seed, 7-day PGI for forage, hay, or straw)									
Soybean forage	0.112-0.186 [125-209][5]	15-44	44	<0.025	0.781	0.723	0.114	0.207	0.212
Soybean hay		21-63	44	<0.030	1.901	1.849	0.119	0.283	0.424
Soybean seed		88-137	44	<0.03	<0.050	0.049	0.032	0.033	0.004
WHEAT (proposed use = 0.267 lb ai/A total application rate, 42-day PGI)									
Wheat forage	0.112 [125][6]	40-98	36	<0.05	<0.21	0.21	0.08	0.08	0.04
Wheat grain		153-183	20	<0.05	<0.05	0.05	0.05	0.05	NA
Wheat straw		153-183	20	<0.06	<0.18	0.18	0.09	0.10	0.04

[1] For the purposes of calculating total residues, HAFT, median, mean, and standard deviation, the LOQ was used for residues reported as <LOQ. Metabolite residues were converted to parent equivalents.
[2] HAFT = Highest average field trial result.
[3] NA = Not applicable.
[4] Applications were made at early postemergence of the crop (~V4 growth stage). Actual application rates ranged 97.6-102.9% of the target rate.
[5] Applications were made at early postemergence of the crop (third trifoliate leaf stage). Actual application rates ranged 96.4-103.9% of the target rate.
[6] Actual application rates were within 1.6% of target rate.

Field and sweet corn

Pyroxasulfone was applied to field corn and sweet corn as an 85% WG formulation at a total of 37 sites in the U.S. representing regions 1, 2, 3, 5, 6, 10, 11 and 12. The application rate was related to soil type: 0.148 lb ai/A (166 g ai/ha) for coarse-textured soil and 0.268 lb ai/A (300 g ai/ha) for medium- and fine-textured soil. The proposed labels specify single application rates up to 0.11 lb ai/A (120 g ai/ha) for coarse-textured soil, up to 0.15 lb ai/A (160 g ai/ha) for medium-textured soil, and up to 0.21 lb ai/A (240 g ai/ha) for fine-textured soil for preplant, preemergence applications, and early postemergence application; a maximum seasonal rate of 0.267 lb ai/A (300 g ai/ha) is proposed (independent of soil type). Therefore, the field trials

conducted at 0.148 lb ai/A represent ~1.3x the proposed maximum single application rate for that soil type and ~0.6x the maximum proposed seasonal rate, and the field trials conducted at 0.268 lb ai/A represent ~1.3x the proposed maximum single application rate for that soil type and ~1x the maximum proposed seasonal rate.

At twenty field corn trials and eleven sweet corn trials, a single postemergence application was made at the rates indicated above at approximately the V4 growth stage of the plant. The field corn trials were conducted in Zones 1 (2 trials), 2 (1 trial), 5 (16 trials), and 6 (1 trial); and the sweet corn trials were conducted in Zones 1 (2 trials), 2 (1 trial), 3 (1 trial), 5 (4 trials), 10 (1 trial), 11 (1 trial), and 12 (1 trial). One field corn trial included an additional plot treated at an exaggerated rate to generate samples for processing; refer to 860.1520 for a discussion of these data. In addition, there were three trials (two field corn and one sweet corn) conducted in Zone 5 that measured residue decline in RAC matrices; applications were made postemergence at ~0.268 lb ai/A at these trials (conducted at sites with fine-textured soils).

At three additional trials with three different soil types (fine, medium, and coarse), five different application types were compared: (1) preplant surface application; (2) preplant incorporated application; (3) post-planting preemergence application; (4) early postemergence application; and (5) split preemergence and postemergence applications. The application rates for types (1), (2), (3), and (4) were 0.268, 0.186, and 0.148 lb ai/A (300, 209, and 166 g ai/ha) for fine, medium, and coarse soils, respectively. The split application was made at 0.178 + 0.089, 0.125 + 0.062, and 0.093 + 0.050 lb ai/A (200 + 100, 140 + 69, and 110 + 56 g ai/ha) for fine, medium, and coarse soils, respectively. For the split application trials, the retreatment interval was 14 to 23 days.

Applications were made in 13-25 gal/A spray volumes using ground equipment; no adjuvant was used.

Duplicate samples of field corn forage were harvested at the late dough/early dent stage, 37-95 days following application. Duplicate samples of sweet corn forage and K+CWHR were collected at normal harvest, 43-132 days following application; sweet corn stover samples were collected 70-132 days following application. Duplicate samples of field corn grain and stover were collected at normal harvest, 85-146 days after application. In the residue decline trials, duplicate forage samples were collected 0, 3, 7, 15-16, 21, 29-30, 40, and 60 days following application; duplicate samples of field corn grain and stover were collected at normal harvest and 15 and 30 days after normal harvest, and duplicate samples of sweet corn K+CWHR and stover were collected at normal harvest and 7 and 14 days following normal harvest.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using the proposed LC/MS/MS enforcement method for corn commodities. The LOQ was 0.005 ppm for each analyte in each commodity. The LOQ for combined residues in parent equivalents was 0.025 ppm for each commodity.

Sample storage conditions and durations are reported in Table 5. The available storage stability data support the field corn field trial study.

The results of the field trials reflecting postemergence application are summarized in Table 8. Residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 were below the LOQ in/on all samples of field corn grain; combined residues in parent equivalents were <0.025 ppm (<0.013 ppm for pyroxasulfone and M-3). In sweet corn K+CWHR samples, residues of pyroxasulfone and its metabolites were below the LOQ in/on all but two samples, from one trial, which had quantifiable residues of M-3 at 0.006 and 0.007 ppm; combined residues were <0.014-0.016 ppm (pyroxasulfone and M-3). Residues of pyroxasulfone were below the LOQ in/on all samples of corn forage, with the exception of two field corn forage samples (residues of 0.010 and 0.012 ppm) and two sweet corn forage samples (residues of 0.006 and 0.007 ppm). Quantifiable residues of M-1 were observed in forage from five of the twenty field corn sites and eight of eleven sweet corn field sites; maximum residues of M-1 were 0.014 ppm in field corn forage and 0.018 ppm in sweet corn forage. Residues of M-3 were below the LOQ in all forage samples, except two samples of sweet corn forage (0.006 ppm in both samples). Quantifiable residues of M 25 were observed in/on forage from six of the twenty field corn sites and eight of eleven sweet corn sites; maximum residues of M-25 were 0.021 ppm in field corn forage and 0.024 ppm in sweet corn forage. Combined residues in parent equivalents ranged <0.025-<0.054 ppm in/on field corn forage and <0.025-<0.063 ppm in/on sweet corn forage.

Residues of pyroxasulfone were below the LOQ in/on all samples of stover, with the exception of one sample each of field corn and sweet corn stover (0.010 ppm in field corn stover and 0.015 ppm in sweet corn stover). Quantifiable residues of M-1 were observed in stover from four of twenty field corn sites and four of eleven sweet corn sites; maximum residues of M-1 were 0.060 ppm for field corn stover and 0.039 ppm for sweet corn stover. Residues of M-3 were below the LOQ in/on all stover samples, with the exception of two field corn stover samples (0.012 and 0.015 ppm), and three sweet corn stover samples (0.005-0.010 ppm). Quantifiable residues of M-25 were observed in stover from two of twenty field corn sites and six of eleven sweet corn sites; maximum residues were 0.029 ppm in field corn stover and 0.044 ppm in sweet corn stover. Combined residues in parent equivalents ranged <0.025-<0.139 ppm in/on field corn stover and <0.025-0.115 ppm in/on sweet corn stover.

The application comparison trials indicated that there were no major differences in residues in samples treated by the different methods and that soil type and environment seemed to have the major influence on residues. Quantifiable residues were only observed in/on forage and stover samples from the application comparison trials conducted on coarse-textured soil. In forage from these trials, samples receiving preplant surface application, early postemergence application, or split preemergence and postemergence applications had similar total residues (<0.119-0.148 ppm), with lower residues found in samples receiving preplant incorporated application or post-planting preemergence application (<0.072-0.085 ppm). In stover, samples from the preplant surface application, preplant incorporated application, early postemergence application, or split preemergence and postemergence applications had similar total residues (<0.070-0.109 ppm), with lower residues found in samples receiving post-planting preemergence application (<0.051 and <0.064 ppm).

The decline trials showed that initial high residues of pyroxasulfone in/on forage immediately after application decline to levels below the LOQ at 30 days after application. Residues of M-1 appeared to increase from the day of application to ~7 days after application, and then decrease after that to below the LOQ by 30 days after application (although quantifiable residues were

observed at 60 days posttreatment at one site, at 0.006 and 0.007 ppm). Residues of M-25 were quantifiable at 3 and 7 days after treatment at all three sites; no residues of M-25 were found after 16 days after treatment. No quantifiable residues of M-3 were found in forage, except in one sample at 60 days posttreatment (0.009 ppm). Residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ in/on all field corn grain and sweet corn K+CWHR samples from the decline trials. No quantifiable residues of pyroxasulfone, M-1, M-3, or M-25 were found in corn stover from the decline trials, except 0.007 ppm M-3 at 15 days after normal harvest from one field corn trial, and 0.010 ppm declining to 0.006 ppm M-1 (over the decline period of 30 days after normal harvest) from the other field corn trial.

Conclusions. The submitted corn data are adequate to satisfy crop field trial data requirements for field and sweet corn. The number and locations of the field trials are in accordance with OPPTS Guideline 860.1500 for field and sweet corn. Field trials were generally conducted at ~1x the proposed maximum seasonal rate, and the application timing represents the latest proposed timing. The petitioner must amend the product label as required per 860.1200 to correlate the maximum seasonal application rate with soil texture.

The available data support the following tolerances for combined residues of pyroxasulfone, M-1, M-3, and M-25 (pyroxasulfone and M-3 for corn grain), expressed as parent equivalents: 0.06 ppm for field corn forage; 0.015 ppm for field corn grain; 0.15 ppm for field corn stover; 0.10 ppm for sweet corn forage; 0.015 ppm for sweet corn K+CWHR; and 0.15 ppm for sweet corn stover; refer to Appendix II for tolerance calculations.

No residue data for aspirated grain fractions were provided. These data are not required to support the proposed use of pyroxasulfone on corn because application is to be made before the reproduction stage begins and seed heads are formed.

No residue data were submitted for popcorn commodities (grain and stover). As the proposed uses on all types of corn are identical, the submitted data for field corn grain and stover may be translated to popcorn grain and stover. Separate tolerances are needed for popcorn commodities. The petitioner must propose tolerances for pyroxasulfone residues of concern in/on popcorn grain, at 0.015 ppm, and popcorn stover, at 0.15 ppm.

Soybean

Pyroxasulfone was applied to soybean, as an 85% WG formulation, at a total of 25 sites in the U.S. representing Zones 2, 4 and 5. The application rate was related to soil type: as low as 0.11 lb ai/A (125 g ai/ha) for coarse-textured soil, up to 0.186 lb ai/A (209 g ai/ha) for medium-textured soil, and up to 0.268 lb ai/A (300 g ai/ha) for fine-textured soil. The proposed labels specify application rates up to 0.11 lb ai/A (120 g ai/ha) for coarse-textured soil and up to 0.21 lb ai/A (240 g ai/ha) for fine-textured soil for preplant/preemergence applications, and up to 0.08 lb ai/A (89 g ai/ha) for coarse-textured soil and up to 0.19 lb ai/A (210 g ai/ha) for fine-textured soil for postemergence application; a maximum seasonal rate of 0.267 lb ai/A (300 g ai/ha) is proposed (independent of soil type).

At twenty trials, a single postemergence application was made at approximately the third trifoliate leaf stage of the plant, at 0.186 lb ai/A (209 g ai/ha) for medium- and fine-textured soils

or at 0.112 lb ai/A (125 g ai/ha) for coarse-textured soils; the application rates represent ~1x and 1.4x the proposed maximum single application rate for this type of application to fine- and coarse-textured soils, respectively, and 0.7x and 0.4x, respectively, the maximum proposed seasonal rate. The trials were conducted in Zones 2 (2 trials), 4 (4 trials), and 5 (14 trials). One trial included an additional plot treated at an exaggerated rate to generate samples for processing; refer to 860.1520 for a discussion of these data. In addition, there were two trials conducted in Zone 5 that measured residue decline in RAC matrices; applications were made postemergence at ~0.186 lb ai/A at these trials (conducted at sites with fine-textured soils).

At three additional trials with three different soil types (fine, medium, and coarse), five different application types were compared: (1) preplant surface application; (2) preplant incorporated application; (3) post-planting preemergence application; (4) early postemergence application; and (5) split preemergence and postemergence applications. The application rates for types (1), (2), and (3) were 0.268, 0.186, and 0.148 lb ai/A (300, 209, and 166 g ai/ha) for fine, medium, and coarse soils, respectively. The application rates for type (4) were 0.186, 0.148, and 0.112 lb ai/A (209, 166, and 125 g ai/ha) for fine, medium, and coarse soils, respectively. The split application was made at 0.178 + 0.089, 0.125 + 0.062, and 0.098 + 0.050 lb ai/A (200 + 100, 140 + 69, and 110 + 56 g ai/ha) for fine, medium, and coarse soils, respectively. For the split application trials, the retreatment interval was 23-26 days.

Applications were made in 10-23 gal/A spray volumes using ground equipment; no spray adjuvant was used.

Duplicate samples were harvested at the R2-R3 stage for forage (15 to 44 days after application), at mid to full bloom for hay (21 to 63 days after application), and at normal harvest for seed (88 to 137 days after application). Hay was field dried to estimated 10-20% moisture content before collection; dry times were not reported. In the residue decline trials, duplicate forage samples were collected 0, 3, 7, 16, 21, 30, and 49-50 days following application; duplicate samples of seed and hay were collected at normal harvest and 5-7, 12-14, and 28-30 days after normal harvest.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using the proposed LC/MS/MS enforcement method for soybean commodities. The LOQ was 0.005 ppm for each analyte in each commodity, with the exception of M-1 in seed for which the LOQ was 0.01 ppm. The LOQ for combined residues in parent equivalents was 0.025 ppm for soybean forage and hay and 0.03 ppm for soybean seed.

Sample storage conditions and durations are reported in Table 5. The available interim storage stability data do not support the soybean field trial study. Additional storage stability data are needed reflecting maximum storage intervals of 12 months for pyroxasulfone, M-1, and M-3 in seed, and 26 months, 24 months, and 29 months for M-25 in forage, seed, and hay, respectively. No additional storage stability data are needed for residues of pyroxasulfone, M-1, or M-3 in soybean forage or hay.

The results of the field trials reflecting postemergence application are summarized in Table 8. Quantifiable residues of pyroxasulfone, M-1, M-3, and M-25 were detected in soybean forage, at <0.005-0.690 ppm for pyroxasulfone, <0.005-0.196 ppm for M-1, <0.005-0.011 ppm for M-3,

and <0.005-0.029 ppm for M-25. Combined residues in parent equivalents ranged <0.025-0.781 ppm in/on soybean forage. Quantifiable residues of pyroxasulfone, M-1, M-3 and M-25 were detected in soybean hay, at <0.005-1.168 ppm for pyroxasulfone, 0.009-0.647 ppm for M-1, <0.005-0.028 ppm for M-3, and <0.005-0.063 ppm for M-25. Combined residues in parent equivalents ranged <0.030-1.901 ppm in/on soybean hay. Residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ in/on all samples of soybean seed, except for three samples, one bearing quantifiable M-25 residues at 0.006 ppm and two bearing quantifiable M-3 residues at 0.016 and 0.017 ppm. Combined residues in parent equivalents ranged <0.03-<0.050 ppm in/on soybean seed.

The application comparison trials generally indicated that early postemergence and split preemergence and postemergence application yielded the highest residues in forage and hay; residues of all analytes were less than or close to the LOQ in/on all seed samples from these trials. Soil type and environment seemed to also have an influence on residues. At the trials conducted on fine- and medium-textured soils, average combined residues resulting from preplant surface, preplant incorporated, or post-planting preemergence applications (<0.028-0.063 ppm in/on forage and <0.041-0.055 ppm in/on hay) were much lower than those resulting from early postemergence and split preemergence and postemergence application (<0.082-0.502 ppm in/on forage and <0.072-0.171 in/on hay). At the trial conducted on coarse-textured soil, there was less difference in average residues; <0.341-0.480 ppm in/on forage and <0.482-0.897 in/on hay from the preplant surface, preplant incorporated, or post-planting preemergence applications versus <0.373-0.501 ppm in/on forage and <0.775-1.169 ppm in/on hay from early postemergence and split preemergence and postemergence application.

The decline trials showed that initial high residues of pyroxasulfone in/on forage immediately after application dissipate rapidly and are below or near LOQ at the times of normal harvest (similar to the residues seen in the majority of the trials). The concentrations of the metabolites M-1 and M-25 increase in forage over time and then generally decrease to concentrations just above LOQ by the final sampling time so at normal harvest intervals, residues could be seen just above LOQ. Residues of M-3 in forage were less than or close to the LOQ in/on all samples. Residues of all analytes were found to decline with increasing sampling intervals in soybean hay. Residues of all analytes were less than or close to the LOQ in/on all seed samples from these trials.

Conclusions. The submitted soybean data are tentatively adequate to satisfy crop field trial data requirements for soybean, pending submission of the final report of the storage stability study. The number and locations of the field trials are in accordance with OPPTS Guideline 860.1500 for soybean. Field trials were generally conducted at ~1x the proposed maximum single application rate and the application timing represents the latest proposed timing. The petitioner must amend the proposed label as specified per 860.1200 to correlate maximum seasonal application rate with soil texture and to reduce the proposed maximum seasonal application rate to conform with the use pattern of the field trials.

It has been determined soybean seed samples need to be reanalyzed for metabolite M-28. After review of residue data, M-28 may need to be added to the tolerance expression. In addition, additional data are required for the soybean use. Once these data are submitted and found adequate, tolerances for soybean RACs will be recommended.

No residue data for aspirated grain fractions were provided. These data are not required to support the proposed use of pyroxasulfone on soybeans because application is to be made before the reproduction stage begins and seed heads are formed.

Wheat

A total of 8 field trials (all of which were decline trials with respect to forage) were conducted in Australia to measure the magnitude of pyroxasulfone residues in/on wheat forage, grain, and straw following either incorporation by sowing (IBS) treatment, or post-sowing preemergence (PSPE) treatment with the 85% WG formulation of pyroxasulfone.

Wheat was treated at 8 locations, reflecting four field trials conducted in 2007-2008 (MRID 47701669) at Yerong Creek, New South Wales; Walla Walla, New South Wales; Roseworthy, South Australia; and Northam, Western Australia; and four feed trials conducted in 2008-2009 (MRID 47701770) at Culcairn, New South Wales; Moree, Northern New South Wales; Templers, South Australia; and Toodyay, Western Australia. In the trials reported in MRID 47701669, separate treatment plots received a single application of the 85% WG formulation at an application rate of 0.112 or 0.223 lb ai/A (125 or 250 g ai/ha) as either an IBS or PSPE treatment; the application rates are 1.4x and 2.8x the maximum proposed single application rate for coarse- and medium-textured soils and 1x and 2x the maximum proposed single application rate for medium-fine and fine soils. In the trials reported in MRID 47701770, the 85% WG was applied to three separate treatment plots at 0.112, 0.134, or 0.223 lb ai/A (125, 150, or 250 g ai/ha) according to the same use patterns; the application rate of 0.134 lb ai/A corresponds to 1.7x the maximum proposed single application rate for coarse- and medium-textured soils and 1.2x the maximum proposed single application rate for medium-fine and fine soils. For the IBS plots, the seed was planted as soon as possible after applying the test substance to the soil; for both IBS and PSPE plots, the seed was planted the same day as test substance application. All applications were made using ground-based equipment, and spray volumes ranged 100-109 L/ha (11-12 gal/A). A control plot was also included for each trial. Although the petitioner provided information pertaining to soil type at each trial, the soil texture (fine, medium, coarse) was not provided. The trials included coarse-, medium-, and fine-textured soils types.

The soil types were identified as red brown earth (three trials), grey clay, gravelly clay, clay loam, loam, and sandy loam (one trial for each of these types). Based on a document found here (http://www.dpi.nsw.gov.au/agriculture/horticulture/vegetables/soil/soilpak), red brown earth soils have a layer of sandy loam to light clay loam overlying clay subsoil. Because the top layer is sandy loam, we considered these soils to be coarse textured.

Single control samples and single or duplicate treated samples of wheat forage, grain, and straw were harvested from both sets of trials. Wheat forage was sampled at PHIs of 28-30, 34-37 and 40-42 days in the trials reported in MRID 47701669. Based on the results from these trials, which did not consistently demonstrate residue decline, forage sampling was extended for the second season of trials reported in MRID 47701670, with wheat forage sampled at PHIs of 41-43, 56-58 and 70-71 days (and 83 and 98 days at one site). The crop growth stage of the wheat plants at forage sampling was not reported. Grain and straw were collected at mature harvest, with PHIs ranging 153-176 days.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using LC/MS/MS Method ATM-0031. The validated LOQ for each analyte was 0.01 ppm in wheat forage, grain, and straw. The LOQ for total residues was 0.05 ppm, expressed as pyroxasulfone equivalents, in all matrices analyzed.

Note that for trials reported in MRID 47701669, samples from both treatment rates (0.112 and 0.223 lb ai/A) were analyzed; however, for trials reported in MRID 47701670, only samples from the 0.112-lb ai/A rate were analyzed for forage, and samples from the 0.112- and 0.134-lb ai/A rates were analyzed for grain and straw.

Sample storage conditions and durations are reported in Table 5. The available interim storage stability data do not support the wheat field trial studies. Additional storage stability data are needed reflecting maximum storage intervals of 13 months for M-25 in forage and 8 months in grain and straw (stover). No additional storage stability data are needed for residues of pyroxasulfone, M-1, or M-3 to support the wheat field trials.

The results of the field trials are summarized in Table 8. The results include both application scenarios, IBS and PSPE. The proposed U.S. label allows both preplant and post-plant preemergence applications. Because trials were conducted by spraying the IBS plots, then planting the entire trial area, then spraying the PSPE plots, all on the same day, the data have been treated as a whole irrespective of application timing in relation to planting.

Total residues of pyroxasulfone and its metabolites generally decreased with time in wheat forage; however, in some trials, a degree of variability was observed going from short to longer sampling times (i.e., higher residues were observed at longer sampling intervals in some cases). Only results reflecting sampling intervals of ≥40 days are included in Table 8, in accordance with the proposed PGI of 42 days for wheat. In forage samples harvested 40-98 days following treatment at 0.112 lb ai/A, residues of pyroxasulfone were below the LOQ in/on all samples with the exception of one in which residues were observed at 0.01 ppm. Residues of M-1, M-3, and M-25 ranged <0.01-0.09, <0.01-0.10, and <0.01-0.04 ppm, respectively. Combined residues ranged <0.05-0.20 ppm in/on forage samples. The moisture content of wheat forage across the trials ranged from 80 to 85%.

Residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ (<0.01 ppm each) in/on all samples of wheat grain harvested 167-183 days following treatment at 0.112 or 0.223 lb ai/A (in the four trials reported in MRID 47701669) and wheat grain harvested 153-176 days following treatment at 0.112 or 0.134 lb ai/A (in the four trials reported in MRID 47701670).

In straw samples harvested 153-183 days following treatment at 0.112 lb ai/A, residues of pyroxasulfone and M-3 were below the LOQ in/on all samples with the exception of one sample in which quantifiable residues of pyroxasulfone were observed at 0.01 ppm. Residues of M-1 and M-25 ranged 0.02-0.09 and <0.01-0.03 ppm, respectively. Combined residues ranged <0.06-0.18 ppm in/on straw samples. The moisture content of wheat hay samples ranged 10.6-22.8%.

Conclusions. The submitted wheat data are not adequate to satisfy data requirements because the geographic representation of the wheat field trials is incomplete. In addition, no samples of

wheat hay were collected in any of the field trials; HED requires residue data and a tolerance for wheat hay to support a use on wheat.

HED has determined that the locations of the 8 Australian field trials correspond to EPA Zones 2, 3, 4, 6, 8, and 10 (based on plant hardiness zones). To support a use on wheat in the U.S. in which quantifiable residues are observed, HED requires a total of 20 field trials, in Zones 1 (1 trial), 2 (1 trial), 5 (5 trials), 6 (1 trial), 7 (5 trials), 8 (6 trials), and 11 (1 trial). Therefore, the petitioner must submit 16 additional field trials on wheat, conducted in Zones 1 (1 trial), 5 (5 trials), 7 (5 trials), 8 (4 trials), and 11 (1 trial). In these trials, the petitioner should collect and analyze samples of wheat forage, hay, grain, and straw; samples should be collected at normal harvest times, and the crop growth stage at harvest should be reported for each sample. The texture of the soil should be reported for each of the field trial sites. If these residue data show that residue levels in forage, grain, and straw are similar to those found in the Australian field trials, HED will not require additional field trial data for wheat hay (i.e., the 16 field trials conducted in the U.S. for wheat hay will be considered sufficient to support a tolerance).

To fully support sample storage conditions and durations, the final report of the ongoing storage stability study with metabolite M-25 must be submitted. No additional storage stability data are needed for pyroxasulfone, M-1, or M-3 to support the wheat field trials.

The study submissions included no raw data for the analytical portion of the study. Raw data from the sample analyses must be submitted; these data should include sample extraction and analysis dates to allow HED to verify sample storage intervals.

No residue data for aspirated grain fractions were provided. These data are not required to support the proposed use of pyroxasulfone on wheat because application is to be made before the reproduction stage begins and seed heads are formed.

Additional data are required for the wheat use. Once these data are submitted and found adequate, tolerances for wheat RACs will be recommended.

860.1520 Processed Food and Feed

Monograph for Pyroxasulfone, Sections B.7.6.1.1 and B.7.7.2 (MRID 47701656; field and sweet corn)
Monograph for Pyroxasulfone, Sections B.7.6.1.2 and B.7.7.2 (MRID 47701657; soybean)

K-I Chemical submitted processing study data for field corn and soybean. No processing study data for wheat were submitted. A summary of the average processing factors found for the processed commodities of field corn and soybean is presented in Table 9.

Table 9. Summary of Processing Factors for Pyroxasulfone.

RAC	Processed Commodity	Processing Factor				
		Pyroxasulfone	M-1	M-3	M-25	Total
Field corn	Grits	NC[1]	NC	NC	NC	--
	Meal	NC	NC	NC	NC	--
	Flour	NC	NC	NC	NC	--
	Starch	NC	NC	NC	NC	--
	Dry-milled Oil	NC	NC	NC	NC	--
	Wet-milled Oil	NC	NC	NC	NC	--
Soybean	Meal	NC	NC	>2.6x[2]	NC	1.4x
	Hulls	NC	NC	>1.4x	NC	0.9x
	Refined oil	NC	NC	NC	NC	--

[1] NC = Not calculated; residues of this analyte were below the LOQ in both the RAC and the processed commodity.
[2] This value exceeds the maximum theoretical concentration of 2.2x for soybean meal.

Field corn

A field corn processing trial was conducted in conjunction with the corn field trials. At one site in IA (fine-textured soil), a single postemergence application of the 85% WG formulation was made to field corn at 1.328 lb ai/A (1488.4 g ai/ha), which is 5x the proposed maximum seasonal rate. A single bulk sample of field corn was collected 136 days following the last application and processed into grits, meal, flour, starch, and wet and dry milled refined oil using simulated commercial processing procedures. Dates of actual processing were not provided; based on sample shipping dates, processing was completed within 133 days of harvest.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using the proposed LC/MS/MS enforcement method for corn commodities. The LOQ was 0.005 ppm for each analyte in each commodity, with the exception of M-3 in meal and M-1 in oil (dry and wet milled) for which the LOQ was 0.01 ppm. The LOQ for combined residues in parent equivalents was 0.025 ppm for grain, grits, flour, and starch, and 0.03 ppm for meal and refined oil.

Sample storage conditions and durations are reported in Table 5. The available storage stability data supports the field corn processing study.

Residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ in/on field corn grain from the exaggerated rate plot. Residues were also below the LOQ in grits, meal, flour, starch, and wet and dry milled oil. Because residues were below the LOQ in all samples, processing factors could not be calculated.

Soybean

A soybean processing trial was conducted in conjunction with the soybean field trials. At one site in IA (fine-textured soil), a single postemergence application of the 85% WG formulation was made to soybeans at 0.571 lb ai/A (640 g ai/ha), which is 3x the proposed maximum single application rate for this type of application. A single bulk sample of soybean seed was collected 113 days following the last application and processed into grits, meal, hulls, and refined oil using

simulated commercial processing procedures. Dates of actual processing were not provided; based on sample shipping dates, processing was completed within 90 days of harvest.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using the proposed LC/MS/MS enforcement method for soybean commodities. The LOQ was 0.005 ppm for each analyte in each commodity, with the exception of M-1 in seed and meal for which the LOQ was 0.01 ppm. The LOQ for combined residues in parent equivalents was 0.025 ppm for soybean hulls and oil and 0.03 ppm for soybean seed and meal.

Sample storage conditions and durations are reported in Table 5. The available interim storage stability data do not support the soybean processing study. Additional storage stability data are needed reflecting maximum storage intervals of 29 months for M-25 in seed, and 16-19 months for M-25 in soybean processed commodities. No additional storage stability data are needed for pyroxasulfone, M-1, and M-3 in soybean processed commodities.

Residues of pyroxasulfone, M-1, M-3, and M-25 were below the LOQ in/on soybean seed from the exaggerated rate plot. Residues were also below the LOQ in meal, hulls and refined oil, except that M-3 was found in soybean meal at 0.013 ppm and in hulls at 0.007 ppm, yielding processing factors of 2.6x for M-3 in meal and 1.4x for M-3 in hulls. Total pyroxasulfone residue (parent, M-1, M-3, and M-25) processing factors would be 1.4x for meal and <1x for hulls. However, M-28 has been determined to be a residue of concern at this time and no processing data has been submitted for M-28. Processing data for M-28 are required. After submittal of these data, the soybean processing study will be re-evaluated for adequacy.

Conclusions. The corn processing study is adequate to satisfy data requirements for corn. However, the soybean processing study is partially adequate to satisfy data requirements for the soybean use. Once the additional data are submitted for the soybean processing study, the adequacy will be determined.

The corn processing data indicate that no quantifiable residues of pyroxasulfone or metabolites M-1, M-3, and M-25 would be expected in field corn processed commodities following treatment at 1x. No tolerances are needed for the processed commodities of field corn.

The soybean processing data indicate that residues of concern for pyroxasulfone concentrate in soybean meal. Using the HAFT of 0.049 ppm, as well as the processing factors of 1.4x, the expected total residues in soybean meal following treatment at 1x would be 0.069 ppm. However, M-28 has been determined to be a residue of concern and no processing data has been submitted for M-28. Processing data for M-28 are required. After submittal of these data, the soybean processing study will be re-evaluated for adequacy.

The interim results of the storage stability study indicate that residues of M-1 may decline in soybean oil during storage (~30% after 7 months of storage). Because the residues of this analyte were below the LOQ in oil processed from seed treated at an exaggerated rate, HED concludes that potential decline during storage is not of concern at this time. This conclusion will be re-evaluated when the final results of the storage stability study have been submitted.

No processing data were submitted for wheat. A processing study for wheat must be submitted as a condition of registration.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for pyroxasulfone and its metabolites M-1, M-3, M-25, M-28, and Metabolite C are not currently available in the EPA National Pesticide Standards Repository (personal communication with Dallas Wright, ACB, 11/18/09). Analytical reference standards of pyroxasulfone and metabolites M-1, M-3, M-25, M-28, and Metabolite C must be supplied and supplies replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of Theresa Cole or Thuy Nguyen at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

(Note that the mail will be returned if the extended zip code is not used.)

860.1850 Confined Accumulation in Rotational Crops

Monograph for Pyroxasulfone, Section B.7.9.1 (MRID 47701674)

The metabolism of pyroxasulfone was investigated in rotated soybean, radish, and wheat. The test substance, radiolabeled pyroxasulfone (pyrazole and isoxazoline labels applied in separate plots), was formulated as a WG formulation and applied to 12 plots (six plots each radiolabel; plus six non-treated plots) containing clay loam soil at a rate equivalent to 0.268 lb ai/A (300 g ai/ha). The application rate is 1x the proposed maximum seasonal rate. The soil surface was treated directly with the formulated product and aged for 30, 120 and 365/490 days (nominal) prior to planting the rotational crops soybean, radish, and wheat. For soybean, the plants in the 365-day isoxazoline-label plot were destroyed by pests, and the plot was replanted at 490 days after treatment. All crops were grown under natural conditions. The petitioner stated that clay loam soil was chosen for the study because the highest application rate on the label is associated with this soil type (fine-textured soil). The petitioner noted that phytotoxicity caused small root samples for radish planted in the 30-day plots.

TRR were >0.01 ppm in all rotated crops matrices from the 30-, 120-, and 365/490-day plantback intervals. The highest residue levels were found in 30-day wheat straw and hay samples, with values as high as 5.2 ppm. The next highest TRR were found in 30-day soybean hay, at 1.2 ppm and 1.6 ppm for isoxazoline and pyrazole labels, respectively. Residues decreased in soybean and radish matrices, and wheat forage, as plantback intervals increased. Residues in wheat hay, straw, and grain matrices declined from the 30-day to 120-day interval but increased slightly or remained at similar levels at 365 days.

The majority of the radioactive residues (generally >70% of TRR) were extracted using conventional organic and polar solvents (ACN, acidic ACN, and 0.1 N NaOH). Additional amounts were extracted using acid, base, lignin and/or enzymatic treatments. Nonextractable

residues after exhaustive extraction were <10% TRR and/or <0.05 ppm in all rotated crop matrices.

For samples collected from plots treated with the pyrazole-label test substance, HPLC and TLC analysis of plant extracts confirmed the presence of parent and two main metabolites (M-1 and M-25), as well as lesser amounts of M-3, M-6, and M-9 in rotated crop matrices. **Pyroxasulfone** was found at levels <5% TRR (<0.01 ppm) in 30-day wheat straw and radish roots and foliage, and 120-day radish roots and foliage; the parent was not detected in any rotated crop matrix at the 365-day plantback interval. **Metabolite M-1** was a major residue accounting for 10-38% TRR in 30-day wheat forage, hay, and straw, soybean forage and hay, and radish roots and foliage (0.031-0.963 ppm); 120-day wheat forage, hay, and straw, soybean forage and hay, and radish foliage (0.013-0.182 ppm); and 365-day wheat forage, hay, and straw, soybean forage and hay, and radish roots and foliage (0.003-0.202 ppm). Metabolite M-1 was found at <10% TRR in all other rotational crop commodities. **Metabolite M-25** (desmethyl M-1) was a major residue accounting for 10-28% TRR in 30-day wheat forage, hay, and straw, and soybean hay; and in 120- and 365-day wheat grain and radish foliage (0.005-0.023 ppm). **Metabolite M-3** was a major metabolite in 30-, 120-, and 365-day wheat grain, at 15-28% TRR (0.008-0.023 ppm), and in 120- and 365-day radish tops, at 11% TRR (0.012 and 0.005 ppm); it was found at <9% TRR in other rotational matrices. **Metabolite M-9** was present at ≤8% TRR, except in 120-day soybean hay, where it was found at 11% TRR (0.118 ppm) and in 365-day soybean forage where it was found at 11% TRR (0.020 ppm). An unknown eluting at 26 minutes (RT26), determined to be **M-9 malonyl glucoside**, was a major residue in 30-day soybean forage and hay, and radish roots, accounting for 16-20% TRR (0.036-0.316 ppm); 120-day soybean forage, hay, and seed, accounting for 10-19% TRR (0.011-0.204 ppm); and 365-day soybean forage and hay, accounting for 12% TRR (0.023 and 0.111 ppm). Another unknown, RT24, which could not be identified, was a major residue in 30-day radish roots (22% TRR, 0.051 ppm), 120-day wheat forage, radish roots, and radish foliage (12-22% TRR, 0.014-0.027 ppm), and 365-day radish roots (10% TRR, 0.003 ppm). The only other identified metabolite, **M-6**, was found at <2.5% TRR in 30-day wheat hay, soybean hay, and radish roots and foliage. These metabolites were formed from the pyrazole portion of the molecule.

For samples collected from plots treated with the isoxazoline-label test substance, several conjugates and cysteine derivatives of the isoxazoline group were detected (metabolites A-D and P1). Metabolites A, B, C, D, P1, and M-28 were major residues (>10% TRR) in these rotated crop matrices at all PBIs: **metabolite A** was found in 30-, 120-, and 365-day wheat and radish matrices (12-45% TRR, 0.01-1.218 ppm); **metabolite B** was found in 30-, 120-, and 365-day wheat and 120-day radish commodities (10-35% TRR, 0.027-1.085 ppm); **metabolite C** was found in 30-, 120-, and 365-day wheat commodities (10-30% TRR, 0.173-0.522 ppm); **metabolite D** was found in 30-, 120-, and 365-day wheat and 120 and 365-day radish commodities (13-29% TRR, 0.01-1.494 ppm); **metabolite P1** was found in 30- and 120-day radish and soybean commodities and 30-day wheat commodities (11-34% TRR, 0.034-0.170 ppm); and **metabolite M-28** was found in 30-, 120-, and 365/490-day wheat and soybean commodities (14-29% TRR, 0.013-0.273 ppm). Parent pyroxasulfone was found at ≤2.5% in 30- and 120-day radish roots and tops, and **metabolite M-6**, the only other identified metabolite, was found at <1% TRR in 30-day wheat hay, soybean seed, and radish foliage and 120-day wheat forage.

Residues of M-1, M-3, and/or M-25 greater than 0.01 ppm were found in rotated radish, soybean, and wheat commodities from the 30- and 120-day PBIs; and in rotated soybean and wheat commodities from the 365-day PBI.

Samples were stored frozen from collection to analysis. Initial HPLC analyses were completed within 58 days of sample collection. No dates of analysis other than initial HPLC analyses were provided. The petitioner stated that repeat analyses of various extracts and isolated products yielded profiles comparable to those initially obtained. No data to support these statements were included in the submission.

Based on the results of the study, the petitioner proposed that in general, metabolism in rotational crops appears to occur via cleavage between the parent sulfone and isoxazoline ring and reaction of glutathione with the isoxazole ring to form a transitory glutathione conjugate (M-15, not observed). Subsequent oxidation and/or demethylation of the pyrazole cleavage product occurred, yielding metabolites M-1, M-3, M-9, and M-25; metabolite M-9 was further conjugated to yield a malonyl glucose conjugate. The transitory glutathione conjugate was further conjugated to another transitory metabolite (M-26, not observed), which underwent further conjugation with malonate and/or glucose to form metabolites A, B, C, D, and M-28; oxidation of M-28 would yield metabolite P-1. Finally, hydroxylation of pyroxasulfone would yield metabolite M-6.

Conclusions. The submitted confined rotational crop study is adequate to satisfy data requirements.

The results of the study indicate that the metabolism of pyroxasulfone in rotated crops is similar to that for primary crops. However, several conjugates and cysteine derivatives of the isoxazoline group (metabolites A, B, C, D, and P1) were found in rotated crops that were not found in primary crops.

The residues of concern in rotational crops for risk assessment at this time are pyroxasulfone and its metabolites M-1, M-3, M-25, M-28, and Metabolite C. The residues of concern for tolerance enforcement cannot be elucidated at this time. No rotation is allowed at this time. Limited/Extensive field rotational crop field studies must be conducted with analysis of pyroxasulfone and its metabolites M-1, M-3, M-25, M-28, and Metabolite C.

860.1900 Field Accumulation in Rotational Crops

Monograph for Pyroxasulfone, Section B.7.9.2 (MRIDs 47701675 and 47701676)

K-I Chemical is not proposing any tolerances for rotated crop commodities in the U.S. The petitioner submitted field rotational crop data from two studies conducted in Australia to support the establishment of rotational crop tolerances in Australia. One study was conducted with field pea at PBIs of 25-28 days, and the other study was conducted with field pea and wheat at PBIs of 348-357 days. The results of the field rotational crop studies are discussed below.

MRID 47701675: Three field rotational crop trials were conducted in Australia to measure the magnitude of total pyroxasulfone residues in field peas planted as a rotational crop 25 to 28 days following the use of the 85% WG formulation on wheat. A single broadcast spray application of the 85% WG formulation was made to soil post-planting preemergence, within 3 days of

planting, to wheat at target rates of 0.134 and 0.223 lb ai/A (150 and 250 g ai/ha) using spray volumes ranging 100-102 L/ha (11 gal/A). The application was made using ground equipment. The wheat crop was treated with glyphosate 21 to 22 days after sowing to achieve "failure" of the wheat crop. Field peas were planted 6 or 7 days later, at a 25 to 28-day PBI. Single control and treated samples of field pea forage, fodder, and seed were collected by hand (forage) or harvester (seed and fodder) at normal commercial harvest; forage was collected at intervals of 42-43, 56-58 and 69-72 days after planting, and fodder and seed were collected 144-159 days after planting. The petitioner noted phytotoxicity in the form of stunted plant growth at two of the three trials; phytotoxicity information was not recorded for the third trial.

The soil textures at the field trial sites were not identified by the petitioner. Based on the soil types, the soil at one of the trials was coarse textured, and the soil at the other two trials was medium textured. The application rates of 0.134 and 0.223 lb ai/A represent 0.5x and 0.8x the proposed maximum seasonal rate for pyroxasulfone.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using LC/MS/MS Method ATM-0031. For calculating total residues, the individual analyte residues were converted to parent molar equivalents and summed. The validated LOQ for each analyte was 0.01 ppm in field pea forage, fodder, and seed. The LOQ for total residues was 0.05 ppm, expressed as pyroxasulfone equivalents, in all matrices analyzed. Note that analysis was restricted to samples treated at a single rate from each site; the 0.134 lb ai/A rate from two sites (coarse- and medium-textured soils), and the 0.223 lb ai/A rate from one site (medium-textured soil).

Sample storage conditions and durations are reported in Table 5. The available interim storage stability data for soybean commodities support the sample storage conditions and durations of the field pea rotational crop study.

Residues of pyroxasulfone and metabolite M-25 were each below the LOQ in/on all samples of field pea forage from crops treated at 0.134 lb ai/A (two sites) and 0.223 lb ai/A (one site). Residues of M-1 were <0.01-0.02 ppm in/on forage from sites treated at 0.134 lb ai/A and were <0.01-0.02 ppm in/on forage from the site treated at 0.223 lb ai/A. Residues of M-3 were below the LOQ in/on forage samples from the sites treated at 0.134 lb ai/A and were <0.01-0.01 ppm in/on forage from the site treated at 0.223 lb ai/A. Combined residues in/on forage ranged <0.05-<0.06 ppm for both treatment rates.

For field pea seed harvested at maturity, residues of pyroxasulfone, M-1, M-3, and M-25 were each below the LOQ in/on all tested samples from all three trial sites. For field pea fodder, residues of pyroxasulfone, M-3, and M-25 were each below the LOQ in/on all tested samples from all three trial sites. Residues of M-1 were 0.05 and 0.08 ppm in/on fodder from sites treated at 0.134 lb ai/A and 0.02 ppm in/on fodder from the site treated at 0.223 lb ai/A. Combined residues in/on fodder ranged <0.05-<0.14 ppm from sites treated at 150 g ai/ha and were 0.06 ppm in/on fodder from the site treated at 0.223 lb ai/A.

MRID 47701676: Four field rotational crop trials were conducted in Australia to measure the magnitude of total pyroxasulfone residues in wheat and field peas grown as rotational crops following the use of the 85% WG formulation on wheat and triticale in the season before

planting of the rotational crops. A single broadcast spray application of the 85% WG formulation was made to the soil either by preplant incorporation or post-planting preemergence to wheat or triticale at target rates of 0.112 and 0.223 lb ai/A (125 and 250 g ai/ha) using spray volumes ranging 100-109 L/ha (11-12 gal/A). These cereal crops were grown to harvest. In the winter season after the cereal harvest, 348-357 days after application, both field peas and wheat were planted at each of the four sites. Single control and treated samples of the wheat forage, grain, and straw, and field pea forage, seed, and fodder were collected by hand (forage) or by harvester (grain, seed, straw, and fodder) at normal commercial harvest times. The forage collection interval for wheat and field pea was 42-43 days after planting. Seed/grain and fodder/straw were sampled at mature harvest, 172-182 days after planting. The petitioner stated that no phytotoxicity effects were observed during the trial period.

The soil textures at the field trial sites were not identified by the petitioner. Based on the soil types, the soil at two of the trials was coarse textured, and the soil at the other two trials was medium textured. The application rates of 0.112 and 0.223 lb ai/A represent 0.4x and 0.8x the proposed maximum seasonal rate for pyroxasulfone.

Samples were analyzed for residues of pyroxasulfone and its metabolites M-1, M-3, and M-25 using LC/MS/MS Method ATM-0031. For calculating total residues, the individual analyte residues were converted to parent molar equivalents and summed. The validated LOQ for each analyte was 0.01 ppm in each commodity. The LOQ for total residues was 0.05 ppm, expressed as pyroxasulfone equivalents, in all matrices analyzed. For forage, analysis of samples from both the 0.112 and 0.223 lb ai/A treatments was conducted; however for fodder/straw and seed/grain, analysis was restricted to samples from the 0.223 lb ai/A treatment.

Sample storage conditions and durations are reported in Table 5. The available interim storage stability data do not support the wheat and field pea rotational crop studies. Additional storage stability data are needed reflecting maximum storage intervals of 8 months for M-25 in wheat forage. No additional storage stability data are needed for residues of pyroxasulfone, M-1, or M-3 to support the field rotational crop trials.

Residues of pyroxasulfone, M-3, and M-25 were below the LOQ in/on all samples of wheat and field pea forage from both treatment rates. In wheat forage from crops treated at 0.112 lb ai/A, residues of M-1 were <0.01-0.02 ppm, and in wheat forage from crops treated at 0.223 lb ai/A, residues of M-1 were <0.01-0.05 ppm. For field peas, no residues of M-1 were found in forage from crops treated at 0.112 lb ai/A; residues of M-1 were <0.01-0.05 ppm in/on samples from the 0.223 lb ai/A treatment. Combined residues in/on wheat forage ranged <0.05-<0.06 ppm for samples treated at 0.112 lb ai/A; and <0.05-<0.10 ppm for samples treated at 0.223 lb ai/A; combined residues in/on pea forage were <0.05 ppm for samples treated at 0.112 lb ai/A and <0.05-<0.10 ppm for samples treated at 0.223 lb ai/A.

In wheat grain and field pea seed harvested at maturity, residues of each analyte were each below the LOQ in/on all samples from the 0.223 lb ai/A treatment plots. For wheat straw and pea fodder, residues of pyroxasulfone, M-3, and M-25 were each below the LOQ in/on all samples from the0.223 lb ai/A treatment plots. Residues of M-1 were 0.02-0.03 ppm in/on wheat straw at three sites, and 0.02 and 0.04 ppm in/on field pea fodder at two sites; residues of M-1 were <0.01

ppm in all other wheat straw and field pea fodder samples. Combined residues in/on wheat straw ranged <0.05-<0.08 ppm and combined residues in/on pea fodder ranged <0.05-<0.09 ppm.

Conclusions. Under the conditions used in the trials, the field rotational crop studies are partially adequate to satisfy data requirements. To fully support storage conditions and durations for forage samples, the final report of the ongoing storage stability study with metabolite M-25 must be submitted.

Although no North American field trials were conducted, the petitioner does not intend to use these data to support rotational crop tolerances in North America. Instead, the petitioner has proposed an 18-month plantback interval for all crops other than corn, soybean, and wheat. The proposed plantback interval is based on the results of the confined rotational crop study, which indicated the potential for quantifiable residues of concern in/on rotated radish, soybean, and wheat commodities from 30- and 120-day PBIs; and in rotated soybean and wheat commodities from a 365-day PBI. The results of the confined rotational crop study indicate that no quantifiable pyroxasulfone residues of concern would be expected in root crops planted 12 months following treatment at 1x the proposed maximum seasonal rate of 0.267 lb ai/A. No data are available demonstrating that residues of concern will be below the LOQ in/on other rotated crop commodities at a PBI of 18 months.

The petitioner must submit a limited field rotational crop study with pyroxasulfone. The study must be conducted in the U.S. and should reflect application at the maximum proposed seasonal rate (0.267 lb ai/A) and planting of rotated crops at plantback intervals 1, 6, and 12 months. If quantifiable residues are found at the 12-month interval, then extensive field trials will be required to set rotational crop tolerances. Pyroxasulfone, M-1, M-3, M-25, M-28, and Metabolite C must be determined in these studies. HED notes that the limited field rotational crop study does not need to include a root crop. If quantifiable residues of concern are observed in rotated crop commodities from the limited field rotational crop study, extensive field rotational crop studies will be required.

Until the required rotational crop data have been submitted, the petitioner must modify the labels for both products to specify that only crops on the label may be planted after pyroxasulfone application; crops on the label may be planted any time after application and root crops after 12 months.

860.1550 Proposed Tolerances

K-I Chemical has proposed that tolerances for pyroxasulfone residues of concern in crop commodities be expressed in terms of combined residues of pyroxasulfone and its major metabolites M-1, M-3, and M-25, calculated as pyroxasulfone. HED has concluded that the proposed tolerance expression is appropriate for corn forage and corn stover. However, the tolerance expression for corn grain should be pyroxasulfone and its metabolite M-3. The tolerance expression for plants should be stated as follows:

> Tolerances are established for residues of the herbicide pyroxasulfone, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum

of pyroxasulfone [3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole] and its metabolites [5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid (M-1), 5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-carboxylic acid (M-3), and [5-(difluoromethoxy)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid (M-25), calculated as the stoichiometric equivalent of pyroxasulfone, in or on the commodity.

There are no Codex MRLs established for residues of pyroxasulfone in any commodities.

The tolerances proposed by K-I Chemical are listed in Table 10, along with the tolerance levels recommended by HED. The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was utilized for determining appropriate tolerance levels for raw agricultural crop commodities; see Appendix II for tolerance calculations.

Adequate field trial data are available to support the proposed tolerances for: corn, field, grain; corn, field, forage; corn, field, stover; corn, sweet, kernel plus cob with husks removed; corn, sweet forage; corn, sweet, stover. The data indicate that the proposed tolerances for field corn grain and sweet corn K+CWHR are too low; tolerances of 0.015 ppm would be appropriate. The data indicate that the proposed tolerances for field corn forage and sweet corn forage are too high; tolerances of 0.06 ppm and 0.10 ppm, respectively, would be appropriate. The available processing data indicate that no tolerances are needed for pyroxasulfone residues in field corn processed commodities.

No residue data were submitted for popcorn commodities (grain and stover). As the proposed uses on all types of corn are identical, the submitted data for field corn grain and stover may be translated to popcorn grain and stover. Separate tolerances are needed for popcorn commodities. The petitioner must propose tolerances for pyroxasulfone residues of concern in/on popcorn grain, at 0.015 ppm, and popcorn stover, at 0.15 ppm

The adequacy of the proposed soybean tolerances will be evaluated pending submission of the final reports of the storage stability studies and additional residue data.

The proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 10.

Table 10. Tolerance Summary for Pyroxasulfone.

Commodity	Proposed Tolerance (ppm)	HED Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Field Corn Grain	0.01	0.015	*Corn, field, grain*
Field Corn Forage	0.15	0.06	*Corn, field, forage*
Field Corn Stover	0.15	0.15	*Corn, field, stover*
Sweet Corn Ears	0.02	0.015	*Corn, sweet, kernel plus cob with husks removed*
Sweet Corn Forage	0.15	0.10	*Corn, sweet, forage*
Sweet Corn Stover	0.15	0.15	*Corn, sweet, stover*
Field Corn Grits	0.01	Remove	Tolerances are not needed for the

Table 10. Tolerance Summary for Pyroxasulfone.

Commodity	Proposed Tolerance (ppm)	HED Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Field Corn Meal	0.01	Remove	processed commodities of corn.
Field Corn Flour	0.01	Remove	
Field Corn Starch	0.01	Remove	
Field Corn Oil (wet and dry milled)	0.01	Remove	
Corn, pop, grain	--	0.015	The submitted data for field corn grain and stover may be translated to popcorn grain and stover
Corn, pop, stover	--	0.15	

Attachments:
Appendix I - Chemical Name and Structure Table
Appendix II - Tolerance Assessment Calculations
Appendix III - REFERENCES

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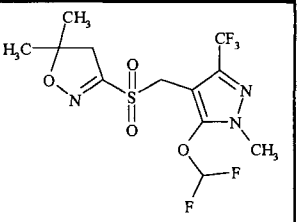
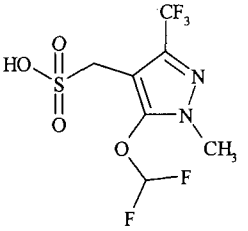
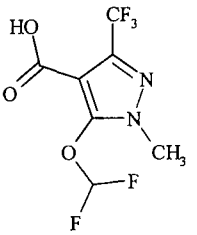
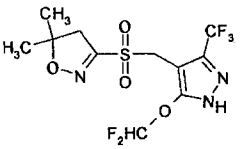
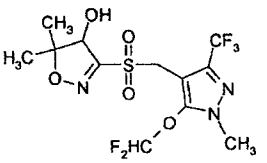
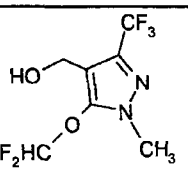
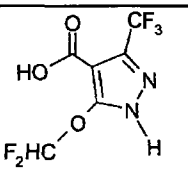
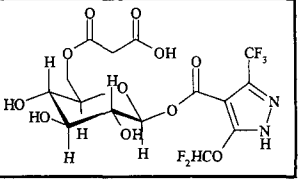
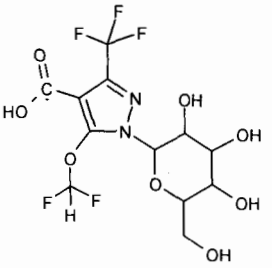
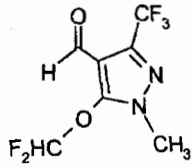
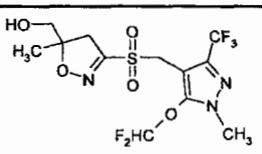
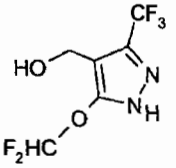
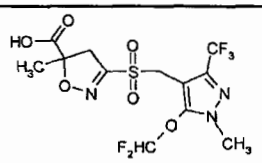
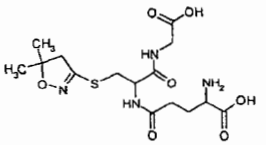
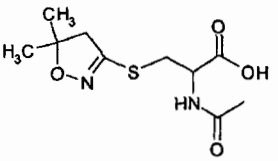
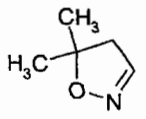
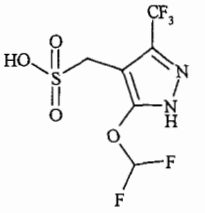
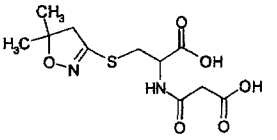
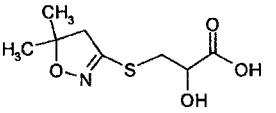
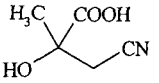
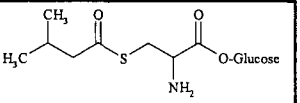
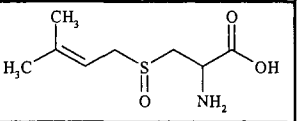
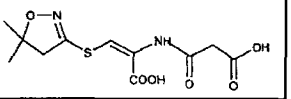
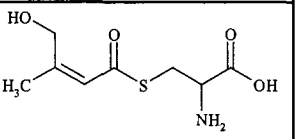
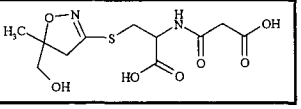
APPENDIX I. Chemical Names and Structures of Pyroxasulfone and Metabolites.			
Code	IUPAC Name	Common Name	Chemical Structure
KIH-485	3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole	Pyroxasulfone	
M-1	[5-(Difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid	N/A	
M-3	5-(Difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-carboxylic acid	N/A	
M-5	3-(5-Difluoromethoxy-3-trifluoromethyl-1*H*-pyrazol-4-ylmethanesulfonyl)-4,5-dihydro-5,5-dimethylisoxazole	N/A	
M-6	3-(5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethanesulfonyl)-4,5-dihydro-5,5-dimethylisoxazol-4-ol	N/A	
M-8	(5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanol	N/A	
M-9	5-Difluoromethoxy-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid	N/A	
M-9 malonyl glucoside (RT26)[1]	None provided	NA	

APPENDIX I. Chemical Names and Structures of Pyroxasulfone and Metabolites.			
Code	IUPAC Name	Common Name	Chemical Structure
N-glycoside of M-9 (Unknown @ 13 mins.)[1]	None provided	NA	
M-10	5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbaldehyde	N/A	
M-11	[3-(5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethanesulfonyl)-4,5-dihydro-5-methylisoxazol-5-yl] methanol	N/A	
M-12	(5-Difluoromethoxy-3-trifluoromethyl-1*H*-pyrazol-4-yl) methanol	N/A	
M-13	3-(5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethanesulfonyl)-4,5-dihydro-5-methylisoxazole-5-carboxylic acid	N/A	
M-15	2-Amino-5-[1-(carboxymethylamino)-3-(5,5-dimethyl-4,5-dihydroisoxazol-3-ylthio)-1-oxopropan-2-ylamino]-5-oxopentanoic acid	N/A	
M-16	2-Acetylamino-3-(5,5-dimethyl-4,5-dihydroisoxazol-3-ylthio)propanoic acid	N/A	
M-22	5,5-Dimethyl-4,5-dihydroisoxazole	N/A	
M-25	[5-(Difluoromethoxy)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanesulfonic acid	N/A	

APPENDIX I. Chemical Names and Structures of Pyroxasulfone and Metabolites.			
Code	IUPAC Name	Common Name	Chemical Structure
M-28	3-[1-Carboxy-2-(5,5-dimethyl-4,5-dihydroisoxazol-3-ylthio)ethylamino]-3-oxopropanoic acid	N/A	
M-29	3-(5,5-Dimethyl-4,5-dihydroisoxazol-3-ylthio)-2-hydroxypropanoic acid	N/A	
M-30[2]	3-cyano-2-hydroxy-2-methylpropanoic acid	N/A	
Metabolite A[1]	None provided (cysteine glucose conjugate of isoxazoline-ring metabolite)	N/A	
Metabolite B[1]	None provided (dimethylpropyl cysteine sulfoxide derivative)	N/A	
Metabolite C[1]	None provided (malonyl dehydrogenated cysteine derivative of isoxazoline group)	N/A	
Metabolite D[1]	None provided (cysteine conjugate of dimethyl acrylic acid)	N/A	
P1[1]	None provided (malonyl cysteine conjugate of isoxazoline-ring products following reaction of pyroxasulfone or metabolites with glutathione)	N/A	

[1] Proposed structure.
[2] Tentatively identified.

Appendix II. Tolerance Assessment Calculations.

For each of the crops listed below, the *OECD MRL Calculator User Guide* (SOP), along with the tolerance spreadsheet, was used for calculating recommended tolerances. As specified in the SOP, the tolerance calculation is in the region of the 95th percentile of the underlying residue distribution, and is more likely to overestimate rather than underestimate the 95th percentile. The rounding procedures specified in the SOP were also used. The OECD tolerance spreadsheet does not require the use of maximum-likelihood estimation (MLE) procedures for values <LOQ.

Field corn

The dataset used to establish a tolerance for pyroxasulfone on field corn commodities consisted of field trial data representing application at the V4 growth stage at 0.148 or 0.268 lb ai/A, depending on soil type, with PHIs of 37-95 days for forage, 69-146 days for grain, and 85-146 days for stover. The field trial application rates are within 25% of the maximum label application rate and the application timing represents the latest proposed timing. The residue values that were entered into the tolerance spreadsheet are provided in Table II-1. The residue values were obtained from the field trials, discussed in the monograph document, in which samples were treated early postemergence (Table B.7.6-1); the results from the "normal" harvest interval in the decline trials (Table B.7.6-3) were included.

Residues of each analyte were below the LOQ in 28 of 44 forage samples, 35 of 44 stover samples, and all 43 grain samples (combined LOQ = 0.025 ppm, pyroxasulfone equivalents, for all matrices). The OECD MRL calculator was used and the recommended tolerances are 0.06 ppm for field corn forage, 0.015 ppm for field corn grain, and 0.15 ppm for field corn stover.

Table II-1. Residue data used to calculate tolerance for pyroxasulfone on field corn forage, grain, and stover.			
Regulator:	EPA	EPA	EPA
Chemical:	Pyroxasulfone	Pyroxasulfone	Pyroxasulfone
Crop:	Field corn forage	Field corn grain	Field corn stover
PHI:	37-95 days	69-146 days	85-146 days
App. Rate:	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A
Submitter:	K-I Chemical	K-I Chemical	K-I Chemical
MRID Citation:	MRID 47701656	MRID 47701656	MRID 47701656
	Combined Residues of Pyroxasulfone and Metabolites M-1, M-3, and M-25 in forage and stover; Pyroxasulfone and M-3 in grain (ppm)[1]		
	<0.025	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.044	<0.013	<0.030
	<0.045	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.054	<0.013	<0.139
	<0.053	<0.013	<0.123
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.029
	<0.028	<0.013	<0.028
	<0.029	<0.013	<0.031

Table II-1. Residue data used to calculate tolerance for pyroxasulfone on field corn forage, grain, and stover.			
Regulator:	EPA	EPA	EPA
Chemical:	Pyroxasulfone	Pyroxasulfone	Pyroxasulfone
Crop:	Field corn forage	Field corn grain	Field corn stover
PHI:	37-95 days	69-146 days	85-146 days
App. Rate:	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A
Submitter:	K-I Chemical	K-I Chemical	K-I Chemical
MRID Citation:	MRID 47701656	MRID 47701656	MRID 47701656
	Combined Residues of Pyroxasulfone and Metabolites M-1, M-3, and M-25 in forage and stover; Pyroxasulfone and M-3 in grain (ppm)[1]		
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.029	<0.013	<0.025
	<0.033	<0.013	<0.039
	<0.032	<0.013	<0.036
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.027		<0.032

[1] Results in which all analytes were below the LOQ are shaded.

Field Corn Forage Region / Country GAP	
Total number of data (n)	22
Percentage of censored data	59%
Number of non-censored data	9
Lowest residue	0.025
Highest residue	0.054
Median residue	0.025
Mean	0.028
Standard deviation (SD)	0.007
Correction factor for censoring (CF)	0.606
Proposed MRL estimate	
- Highest residue	0.054
- Mean + 4 SD	0.057
- CF x 3 Mean	0.051
Unrounded MRL	0.057
Rounded MRL	**0.06**
High uncertainty of MRL estimate. [High level of censoring]	

Residues (mg/kg)	n
< 0.025	13
0.025	1
0.027	1
0.028	2
0.029	2
0.033	1
0.045	1
0.054	1

Field Corn Stover Region / Country GAP	
Total number of data (n)	22
Percentage of censored data	73%
Number of non-censored data	6
Lowest residue	0.025
Highest residue	0.131
Median residue	0.025
Mean	0.031
Standard deviation (SD)	0.023
Correction factor for censoring (CF)	0.515
Proposed MRL estimate	
- Highest residue	0.131
- Mean + 4 SD	0.121
- CF x 3 Mean	0.048
Unrounded MRL	0.131
Rounded MRL	**0.15**
High uncertainty of MRL estimate. [High level of censoring]	

Residues (mg/kg)	n
< 0.025	16
0.027	1
0.028	1
0.029	1
0.03	1
0.038	1
0.131	1

Pyroxasulfone Field Corn Grain

Region / Country	
GAP	
Total number of data (n)	20
Percentage of censored data	100%
Number of non-censored data	0
Lowest residue	0.013
Highest residue	0.013
Median residue	0.013
Mean	0.013
Standard deviation (SD)	0.000
Correction factor for censoring (CF)	0.333
Proposed MRL estimate	
- Highest residue	0.013
- Mean + 4 SD	0.013
- CF x 3 Mean	0.013
Unrounded MRL	0.013
Rounded MRL	**0.015**
High uncertainty of MRL estimate. [High level of censoring]	

Residues (mg/kg)	n
< 0.013	20

Sweet corn

The dataset used to establish a tolerance for pyroxasulfone on sweet corn commodities consisted of field trial data representing application at the V4 growth stage at 0.148 or 0.268 lb ai/A, depending on soil type, with PHIs of 43-97 days for forage, 43-132 days for K+CWHR, and 70-132 days for stover. The field trial application rates are within 25% of the maximum label application rate, and the application timing represents the latest proposed timing. The residue

values that were entered into the tolerance spreadsheet are provided in Table II-2. The residue values were obtained from the field trials, discussed in the monograph document, in which samples were treated early postemergence (Table B.7.6-1); the results from the "normal" harvest interval in the decline trials (Table B.7.6-3) were included.

For sweet corn commodities, residues of each analyte were below the LOQ in 5 of 24 forage samples, 22 of 24 K+CWHR samples, and 13 of 24 stover samples (combined LOQ = 0.025 ppm, pyroxasulfone equivalents, for all matrices (0.013 ppm for K+CWHR pyroxasulfone and M-3)).
Using the OECD MRL calculator, the recommended tolerances are 0.10 ppm for sweet corn forage, 0.15 ppm for sweet corn stover, and sweet corn K+CWHR is 0.015 ppm.

Table II-2. Residue data used to calculate tolerance for pyroxasulfone on sweet corn forage, K+CWHR, and stover.

Regulator:	EPA	EPA	EPA
Chemical:	Pyroxasulfone	Pyroxasulfone	Pyroxasulfone
Crop:	Sweet corn forage	Sweet corn K+CWHR	Sweet corn stover
PHI:	43-97 days	43-132 days	70-132 days
App. Rate:	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A
Submitter:	K-I Chemical	K-I Chemical	K-I Chemical
MRID Citation:	MRID 47701656	MRID 47701656	MRID 47701656
	Combined Residues of Pyroxasulfone and Metabolites M-1, M-3, and M-25 (ppm)[1]		
	<0.038	<0.013	<0.028
	<0.039	<0.013	<0.045
	<0.063	<0.013	<0.025

Table II-2. Residue data used to calculate tolerance for pyroxasulfone on sweet corn forage, K+CWHR, and stover.			
Regulator:	EPA	EPA	EPA
Chemical:	Pyroxasulfone	Pyroxasulfone	Pyroxasulfone
Crop:	Sweet corn forage	Sweet corn K+CWHR	Sweet corn stover
PHI:	43-97 days	43-132 days	70-132 days
App. Rate:	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A	0.148-0.268 lb ai/A
Submitter:	K-I Chemical	K-I Chemical	K-I Chemical
MRID Citation:	MRID 47701656	MRID 47701656	MRID 47701656
	Combined Residues of Pyroxasulfone and Metabolites M-1, M-3, and M-25 (ppm)[1]		
	<0.063	<0.013	<0.025
	<0.050	<0.013	<0.075
	<0.047	<0.013	<0.088
	<0.025	<0.013	<0.025
	<0.025	<0.013	<0.025
	<0.025	<0.013	0.115
	<0.026	<0.013	<0.109
	<0.042	<0.014	<0.025
	<0.042	<0.016	<0.025
	<0.034	<0.013	<0.025
	<0.035	<0.013	<0.025
	<0.028	<0.013	<0.025
	<0.029	<0.013	<0.025
	<0.034	<0.013	<0.025
	<0.033	<0.013	<0.025
	<0.025	<0.013	<0.053
	<0.025	<0.013	<0.053
	<0.029	<0.013	<0.031
	<0.025	<0.013	<0.032
	<0.031	<0.013	<0.025
	<0.025	<0.013	<0.025

[1] Results in which all analytes were below the LOQ are shaded.

Pyroxasulfone
Sweet Corn Forage

Region / Country	
	GAP
Total number of data (n)	12
Percentage of censored data	17%
Number of non-censored data	10
Lowest residue	0.025
Highest residue	0.063
Median residue	0.032
Mean	0.035
Standard deviation (SD)	0.012
Correction factor for censoring (CF)	0.889
Proposed MRL estimate	
- Highest residue	0.063
- Mean + 4 SD	0.081
- CF x 3 Mean	0.094
Unrounded MRL	0.094
Rounded MRL	0.1

Residues (mg/kg)	n
< 0.025	2
0.026	1
0.027	1
0.028	1
0.029	1
0.034	1
0.035	1
0.039	1
0.042	1
0.049	1
0.063	1

Pyroxasulfone
Sweet Corn Stover
Region / Country
GAP

Total number of data (n)	12
Percentage of censored data	50%
Number of non-censored data	6
Lowest residue	0.025
Highest residue	0.112
Median residue	0.025
Mean	0.041
Standard deviation (SD)	0.028
Correction factor for censoring (CF)	0.667
Proposed MRL estimate	
- Highest residue	0.112
- Mean + 4 SD	0.154
- CF x 3 Mean	0.082
Unrounded MRL	0.154
Rounded MRL	0.15

Residues (mg/kg)	n
< 0.025	6
0.025	1
0.032	1
0.037	1
0.053	1
0.082	1
0.112	1

Pyroxasulfone
Sweet corn K+CWHR
Region / Country
GAP

Total number of data (n)	12
Percentage of censored data	92%
Number of non-censored data	1
Lowest residue	0.013
Highest residue	0.015
Median residue	0.013
Mean	0.013
Standard deviation (SD)	0.001
Correction factor for censoring (CF)	0.389
Proposed MRL estimate	
- Highest residue	0.015
- Mean + 4 SD	0.015
- CF x 3 Mean	0.015
Unrounded MRL	0.015
Rounded MRL	**0.015**
High uncertainty of MRL estimate. [High level of censoring]	

Residues (mg/kg)	n
< 0.013	11
0.015	1

Appendix III. REFERENCES

DP#: D389415
Subject: **Pyroxasulfone.** Review of Residue Data for the New Active Ingredient Pyroxasulfone.
From: T. Morton
To: M. Walsh
Dated: 5/12/11
MRIDs: 48430006 & 48430011

DP#: D389651
Subject: **Pyroxasulfone.** Review of Enforcement Method Amendments for the New Active Ingredient Pyroxasulfone.
From: T. Morton
To: M. Walsh
Dated: 5/25/11
MRIDs: 48430001

DP#: D394353
Subject: **Pyroxasulfone.** Review of Residue Data for the New Active Ingredient Pyroxasulfone.
From: T. Morton
To: M. Walsh
Dated: 10/13/11
MRIDs: 48430015

DP#: D395720
Subject: **Pyroxasulfone.** Review of Residue Data for the New Active Ingredient Pyroxasulfone.
From: T. Morton
To: M. Walsh
Dated: 11/17/11
MRIDs: 48430009 & 48430010

DP#: D396692
Subject: **Pyroxasulfone.** Review of Residue Data for the New Active Ingredient Pyroxasulfone.
From: T. Morton
To: M. Walsh
Dated: 12/8/11
MRIDs: 48466203